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Advances in the chemical and biological diversity of heterocyclic systems incorporating pyrimido[1,6-*a*] pyrimidine and pyrimido[1,6-*c*]pyrimidine scaffolds

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Heterocycles incorporating a pyrimidopyrimidine scaffold have aroused great interest from researchers in the field of medical chemistry because of their privileged biological activities; they are used as anti-bacterial, antiviral, anti-tumor, anti-allergic, antihypertensive, anticancer, and hepatoprotective agents. Therefore, the present study aims to investigate the chemistry of heterocycles incorporating pyrimido[1,6-*a*]pyrimidine and pyrimido[1,6-*c*]pyrimidine skeletons and their biological characteristics. The main sections discuss (1) the synthetic routes to obtain substituted pyrimidopyrimidines, pyrimido[1,6-*a*]pyrimidin-diones, pyrimidoquinazolines, tricyclic, tetracyclic, and binary systems; (2) the reactivity of the substituents attached to the pyrimidopyrimidine skeleton, including thione and amide groups, nucleophilic substitutions, condensations, ring transformations, and coordination chemistry; (3) compounds of this class of heterocycles containing a significant characteristic scaffold and possessing a wide range of biological characteristics.

1. Introduction

Due to their various substantial biological characteristics, pyrimidopyrimidine compounds have recently established a notable place in the work of researchers in the field of

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medicinal chemistry.[1] Pyrimido[4,5-*d*]pyrimidines are used as cancer cell growth inhibitors,[2] antioxidants,[3] agents to reduce dihydrofolic acid to tetrahydrofolic acid,[4] antidiabetics,[5] angiogenesis inhibitors,[6] resistance modification agents,[7] *Mycobacterium tuberculosis*,[8] hypertension,[9] and allergy symptom treatments,[10] antibacterial[11] and antiviral agents,[12] antitumor agents that inhibit monocarboxylate transporters (MCTs),[13–15] anti-inflammatory[16] and hepatoprotective agents,[17] and tyrosine kinase inhibitors.[18] The pyrimidopyrimidines of this class comprise 4*H*-pyrimido[1,6-*a*]pyrimidine, 6*H*-pyrimido [1,6-*a*]-pyrimidine, and 1*H*-pyrimido[1,6-*c*]pyrimidine (Fig. 1) and their fused benzene derivatives. Accordingly, the analogs pyrimido[1,2-*c*]pyrimidines are a class of 4*H*-pyrimido[1,6-*a*] pyrimidines. Sirakanyan *et al.*[19] reported the synthesis of a pentacyclic system, pyranopyridofuro[2,3-*e*]pyrimido[1,2-*c*] pyrimidine, in 71% yield by the chlorination of the desired pyrimidine-aminoalcohol with phosphorus oxychloride and subsequent intramolecular cyclization under reflux conditions. Moreover, Vivek's group[20] prepared a series of tricyclic systems, ethyl 8-substituted-10-(methylthio)-4-oxo-4,8-dihydropyrazolo [4,3-*e*]pyrimido[1,2-*c*]pyrimidine-3-carboxylates, by the reactions of 1-substituted-3-(methylthio)-1*H*-pyrazolo-[3,4-*d*] pyrimidin-4-amines with diethyl 2-(ethoxymethylene)malonate under either solvent-free microwave irradiation (81–85%) or thermal conditions (51–62%) in diphenyl ether. Tanarro and Gutschow[21] reported the synthesis of 10-benzyl-3,4,9,10,11,12-hexahydro-2*H*-pyrido[4′,3′:4,5]thieno[3,2-*e*]-pyrimido[1,2-*c*] pyrimidine from ethyl 2-amino-6-benzyl-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylate and evaluated its activity as an inhibitor for acetyl-cholinesterase from EeAChE, hAChE, and hBChE.

4*H*-Pyrimido[1,6-*a*]pyrimidines are rarely reported despite the fact they provide an exceptional ring structure and multiple substitution designs, polarities, and H-bonding proficiencies. In view of this, 4*H*-pyrimido[1,6-*a*]pyrimidin-4-ones were obtained by the condensation of 4-aminopyrimidine with Meldrum's acid[22] or ethyl acetoacetate.[23] Kitagawa's group[24] reported the synthesis of 2,3,4,7-tetrahydro-6*H*-pyrimido[1,6-*a*] pyrimidin-6-one (50% yield) and its 8-methyl analog (15% yield) as cyclization products by the treatment of both 2,4-dichloro-pyrimidine and 2,4-dichloro-6-methylpyrimidine with 3-aminopropan-1-ol and subsequent treatment with thionyl chloride in tetrahydrofuran; an additional product was formed (62% yield) due to the chlorination of the 8-methyl analog at C9 of the pyrimidopyrimidinone ring. Lulle *et al.*[25] conveyed the synthesis of 1-substituted-1,2,3,4-tetrahydro-6*H*-pyrimido[1,6-*a*]

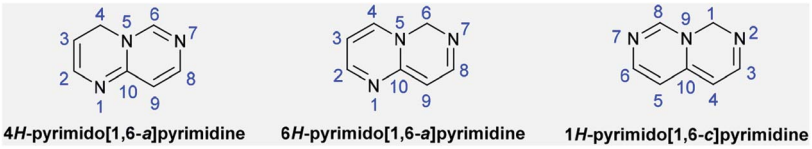

Fig. 1 Structures and atomic numbering of the 4*H*-, 6*H*-pyrimido[1,6-*a*]pyrimidine and 1*H*-pyrimido[1,6-*c*]pyrimidine skeletons.

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pyrimidine-6,8(7*H*)-diones by the amination of 1-(3-bromopropyl)-pyrimidine-2,4(1*H*,3*H*)-dione with different amines, such as ammonia, propylamine, butylamine, and benzylamine, and subsequent intramolecular cyclization. Previously, methyl 2-benzoylamino-3-dimethylaminopropenoate served as a synthon for the preparation of *N*-(6,8-dihydroxy-4-oxo-4*H*-pyrimido[1,6-*a*]pyrimidin-3-yl)benzamide from heterocyclic α-amino compounds in acetic acid.[26] A series of 1,4,9*b*-triazaphenalenes as types of pyridopyrimido[1,6-*a*]pyrimidines were synthesized by the thermal condensation reactions of 3-substituted-cyclopropane-1,1,2,2-tetracarbonitriles in 1,2-dichlorobenzene at reflux temperatures, and their potential as materials for electronic applications was studied.[27] In addition, the conformers of perhydro-3a,6a,9a-triazaphenalene were studied by stereoelectronic stabilization, gauche interactions, DFT calculations, and spectral data.[28]

A book chapter by Vasvári-Debreczy *et al.* described the chemistry of bicyclic heterocyclic systems of the type [6 + 6] containing a nitrogen atom at the ring junction.[29a] One of the heterocyclic compounds investigated in this chapter incorporated a pyrimido[1,6-*a*]pyrimidine scaffold. In this chapter, the researchers discussed the synthesis of pyrimido[1,6-*a*]pyrimidine-6-thione, pyrimido[1,6-*a*]quinazolinone, pyrimido[1,2-*c*]quinazoline, pyrimido[6,1-*b*]quinazolinone, and pyrimido-[5,6,1-*ij*]quinazolinone heterocyclic systems. Hermecz and Vasvári-Debreczy wrote a book chapter on 6-6 bicyclic systems with a ring junction nitrogen atom, in which the synthesis of 2*H*-pyrimido[1,6-*a*]pyrimidines was briefly discussed.[29b]

On the other hand, Elattar *et al.* reviewed the chemistry of pyrimido[1,2-*a*]pyrimidines,[30] pyrimido[4,5-*b*]pyrimidines, and pyrimido[5,4-*b*]pyrimidines.[31] The pyrimido[1,2-*a*]-pyrimidines[30] were synthesized from the reaction of guanidine with ethyl 2-methyl-3-oxopropanoate, unsaturated ketones or unsaturated nitriles. Acid treatment of dihydro-4*H*-pyrimido[1,2-*a*]pyrimidines led to the formation of pyrimidopyrimidinium salts. In addition, pyrimido[1,2-*a*]pyrimidines were synthesized from amino-pyrimidines by multicomponent reactions with aryl aldehydes and barbituric or thiobarbituric acids, substituted-dihydro-3*H*-pyrazol-3-ones or active nitriles. The reactions of β-ketoesters with amino-pyrimidines yielded the anticipated ring systems; also, the reactions of alkynones, diesters or enaminoesters with aminopyrimidines yielded the same target heterocycles. In another route, pyrimido[2,1-*b*]quinazolinones are a type of pyrimido[1,2-*a*]pyrimidines which are prepared by ring transformation of 6-amino-3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolines; moreover, thienyl-pyrimido[1,2-*a*]pyrimidines are analgesic and antimicrobial agents. Also, the salts of these compounds are inhibitors of human platelet aggregation, and the tricyclic systems are potent gastroprotective agents. 3,8-diaryl-4*H*-pyrimido[1,2-*a*]pyrimidinone has antagonistic effects on melanin-concentrating hormone receptor and pyrimido[1,2-*a*]quinazolinones are protein kinase inhibitors. Additionally, dipyridamole, a type of pyrimido[5,4-*d*]pyrimidine,[31] is an anticoagulant agent and cAMP-phosphodiesterase platelet inhibitor; it also decreases pulmonary hypertension.[32] The present study aims to explore and investigate the chemistry of pyrimido[1,6-*a*]pyrimidines and pyrimido[1,6-*c*]pyrimidines as important classes of heterocycles and to inspect their diverse biological activities. This is considered to be a complementary study to our previous studies in this field,[33–37] which are considered to be an addition to the field of medicinal chemistry.

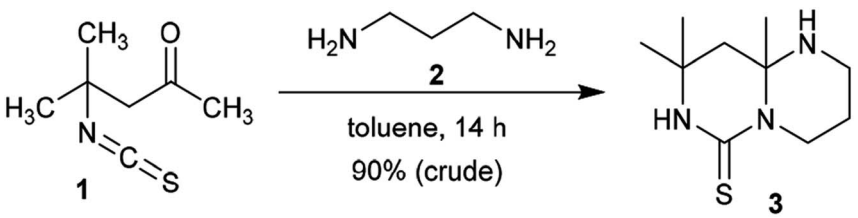
2. Synthetic methods

2.1. Synthesis of substituted pyrimidopyrimidines

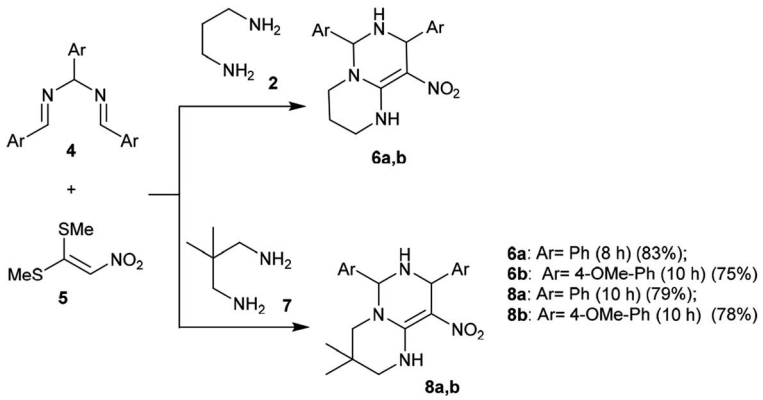
2.1.1. Synthesis from acyclic reactants. In light of observations, 4-isothiocyanato-4-methylpentan-2-one (**1**) was reacted with propane-1,3-diamine (**2**) in a molar ratio of 3 : 1 to afford the anticipated product, pyrimidopyrimidine-thione **3**, in excellent yield. The product was formed based on the molar ratio of the reactants. The functional group of the substituent in position 1 was ring-closed to afford binuclear junction **3**. The condensed heterocycle **3** was formed by preliminary condensation of the amino function of the diamine with the ketonic carbonyl function of 4-isothiocyanato-4-methylpentan-2-one (**1**), followed by a subsequent intramolecular nucleophilic attack of the terminal amino function at the C=S function of the isothiocyanate fragment (Scheme 1).[38]

A proficient synthetic route was reported by Alizadeh *et al.*[39] through a multicomponent procedure. Subsequently, the reactions of (2-nitroethene-1,1-diyl)*bis*(methylsulfane) (**5**) with propane-1,3-diamine (**2**) or 2,2-dimethylpropane-1,3-diamine (**7**) followed by reaction with *N*,*N*′-(arylmethylene)*bis*(1-arylmethanimine) (**4**) at reflux temperature yielded the desired diaryl-hexahydro-2*H*-pyrimidopyrimidines **6a**, **6b**, **8a**, and **8b**, respectively, with yields ranging from 75%–83% (Scheme 2). This procedure offers an alternative technique for application in drug discovery.[39]

The proposed mechanism of these reactions was demonstrated through nucleophilic substitution of the amino groups of acyclic diamines with methyl-mercaptan groups to generate



Scheme 1 Synthesis of 8,8,9a-trimethyloctahydro-6*H*-pyrimidopyrimidine-thione.



Scheme 2 Synthesis of hexahydro-2*H*-pyrimido[1,6-*a*]-pyrimidines.

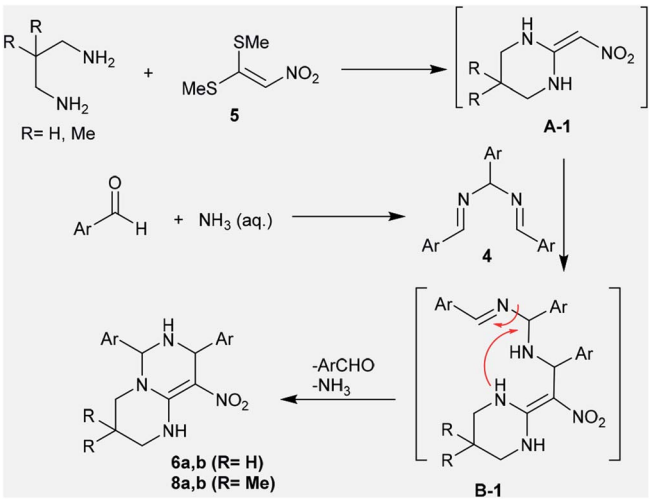
the first pyrimidine ring (intermediate **A-1**). Next, the addition of the intermediate **A-1** to *N*,*N*′-(arylmethylene)*bis*(1-arylmethanimine) (**4**) generated the intermediate **B-1**, which underwent successive cyclization to afford the products **6** and **8** through the elimination of aryl aldehyde and ammonia molecules by a hydrolysis step. The general mechanism involved the cycloaddition of diamines to *bis*-methylsulfane **5**, attack of the generated intermediate at the C=N bond of compound **4**, and subsequent intramolecular cyclization to construct another pyrimidine ring (Scheme 3).[39]

2.1.2. Multicomponent synthesis. Multicomponent reactions were employed for the synthesis of ethyl 2,4,8,9-tetrasubstituted-4*H*-pyrimido[1,6-*a*]pyrimidine-3-carboxylates through a facile synthetic route. In this route, one-pot three-component reactions of aminopyrimidines **9** and aldehydes **10** with β-ketoesters **11** yielded the respective ethyl carboxylates **12**. The compounds contain an sp^3 carbon at the C4 position, which diminishes the aromaticity of the 6–6 bicyclic system. Additionally, the chlorine atom and amino group ($R_1 = Cl$, $R_2 = NH_2$) increase the diversity of structures **12a–p**. The reactions of **10a** with **11a** and **9a** to prepare ethyl carboxylate **12a** were carried out using different acids, such as hydrochloric acid, sulfuric acid, and trifluoromethane–sulfonic acid, in different equivalent amounts using acetonitrile as a solvent and by solvent-free reactions. As a result, better product yields were achieved under solvent-free conditions with trifluoromethanesulfonic acid (0.5 equiv.) by heating at 110 °C. In the first step, the aldehydes **10** were condensed with the respective β-ketoesters **11** to form the arylidene intermediates, which reacted with the aminopyrimidines to afford the desired ethyl carboxylates **12** (Scheme 4).[40]

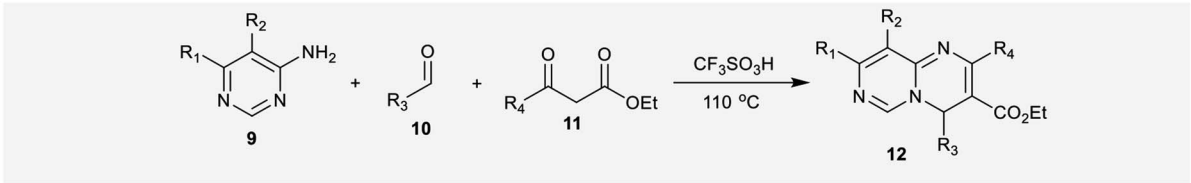
2.1.3. Synthesis from 4-aminopyrimidines. Heating 5-(benzyloxy)pyrimidin-4-amine (**13**) and 5-methoxypyrimidin-4-amine (**14**) with diethyl 2-(ethoxymethylene)malonate yielded the respective enamines **15** and **16**, respectively, in excellent yields (88% and 85%) after elimination of an ethanol molecule. Cyclization of the enamines **15** and **16** was accomplished by heating with Dowtherm reagent to afford ethyl carboxylates **17a** and **17b** in moderate yields. The cyclization step proceeded through an initial rearrangement involving a[1,3] H shift followed by an intramolecular nucleophilic attack of the formed imine at the carbonyl ester group and subsequent elimination of an ethanol molecule. Hydrogenolysis of pyrimido[1,6-*a*]pyrimidine **17b** with catalytic palladium over carbon or palladium hydroxide produced the desired ethyl carboxylate **18** through the cleavage of O–C bonds with the elimination of a benzyl alcohol molecule (Scheme 5).[22]

Similarly, the condensation of 4-alkoxy-4-aminopyrimidines **13** and **14** with Meldrum's acid derivative afforded, after thermal cyclization, the enaminoester intermediates **19** and **20** with the formation of 9-alkoxy-1-pyrimido[1,6-*a*]pyrimidines **21a** and **21b** substituted by a 3-ethoxycarbonyl group in the first issue. The hydrogenolysis of the anticipated benzyl ether afforded 9-hydroxy-4*H*-pyrimido[1,6-*a*]pyrimidin-4-one **22** as a heterocyclic phenol and the analog ketone **23** (Scheme 6).[22]

The previous procedure was applied for acyclic ketones such as sodium oxobutenolate **25** and sodium propenolate **27**. Therefore, 6-aminothiouracil (**24**) was subsequently reacted with sodium salts **25** and **27** in piperidine acetate at their reflux temperatures to afford the desired 4-substituted-

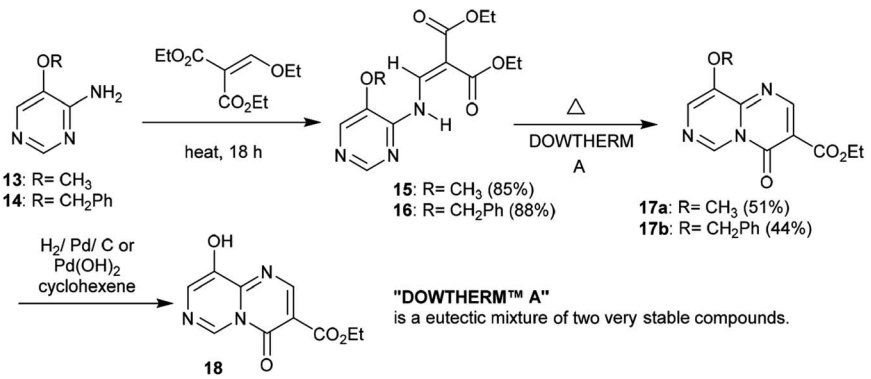


Scheme 3 The proposed mechanism for the ring construction of pyrimidopyrimidines **6** and **8**.



Compound 12	R_1	R_2	R_3	R_4	Yield %
a	Cl	NH_2	Ph	CH_3	63
b	Cl	NH_2	4-OCH_3-Ph	CH_3	38
c	Cl	NH_2	4-CH_3-Ph	CH_3	55
d	Cl	NH_2	3-CH_3-Ph	CH_3	46
e	Cl	NH_2	2-CH_3-Ph	CH_3	50
f	Cl	NH_2	4-Cl-Ph	CH_3	58
g	Cl	NH_2	4-Br-Ph	CH_3	61
h	Cl	NH_2	4-F-Ph	CH_3	56
i	Cl	NH_2	4-CN-Ph	CH_3	43
j	Cl	NH_2	4-NO_2-Ph	CH_3	53
k	Cl	NH_2	thien-2-yl	CH_3	35
l	Cl	NH_2	naphth-1-yl	CH_3	44
m	Cl	NH_2	*n*-Pr	CH_3	29
n	Cl	NH_2	cyclopropyl	CH_3	31
o	Cl	NH_2	Ph	Et	40
p	Cl	NH_2	Ph	Ph	10
q	Cl	H	Ph	Ph	traces
r	H	H	Ph	CH_3	traces
s	piperidin-1-yl	H	Ph	CH_3	65

Scheme 4 Multicomponent synthesis of ethyl 2,4,8,9-tetrasubstituted-4*H*-pyrimido[1,6-*a*]pyrimidine-3-carboxylates.



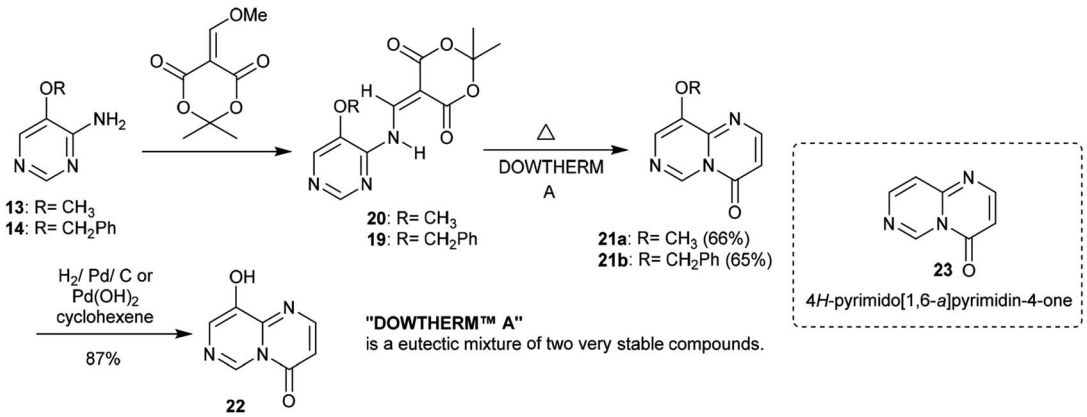
Scheme 5 Synthesis of the ethyl carboxylate of pyrimidopyrimidine **18**.

pyrimidopyrimidinones **26** and **28**, respectively. The proposed mechanistic route adopted to obtain these compounds proceeded according to the same mechanism proposed for the formation of cycloalkyl[*e*]pyrimido[1,6-*a*]pyrimidin-3(7*H*)-ones (Scheme 7).[41]

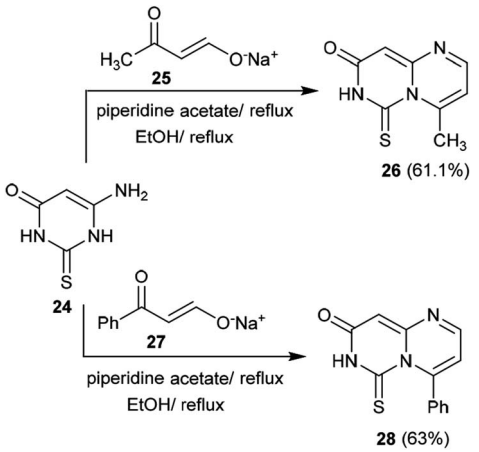
Condensation of Meldrum's acid with methyl formate catalyzed by zinc chloride provided a facile *in situ* preparation of its methoxy-methylene derivative **30**. Consequently, 5-(benzyloxy) pyrimidin-4-amine (**29**) was reacted with a derivative of Meldrum's acid (**30**) to afford the pyrimidinyl-dioxane-dione **31** in a yield of 68%. The respective pyrimidopyrimidinone **32** was generated by heating compound **31** to release carbon dioxide and acetone molecules. Hydrogenolysis of **32** using a palladium over carbon system led to removal of the protecting benzyl group to afford 9-hydroxy-4*H*-pyrimido[1,6-*a*]pyrimidin-4-one (**33**) (Scheme 8).[42]

2.2. Synthesis of pyrimido[1,6-*a*]pyrimidin-diones

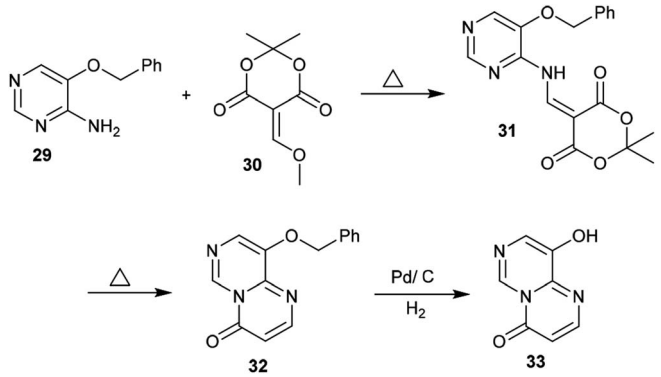
2.2.1. Ring annulation attempts. The enaminone derivative of 2*H*-naphtho[1,4] oxazinone (**34**) was reacted with 6-amino-2-thioxo-2,3-dihydro-pyrimidin-4(1*H*)-one (**24**) and 6-amino-pyrimidine-2,4(1*H*,3*H*)-dione (**35**), respectively,[43] by heating in



Scheme 6 Synthesis of 9-hydroxy-4*H*-pyrimido[1,6-*a*]pyrimidin-4-one.



Scheme 7 Synthesis of 4-substituted-6-thioxo-6,7-dihydro-8*H*-pyrimido[1,6-*a*]pyrimidin-8-ones.



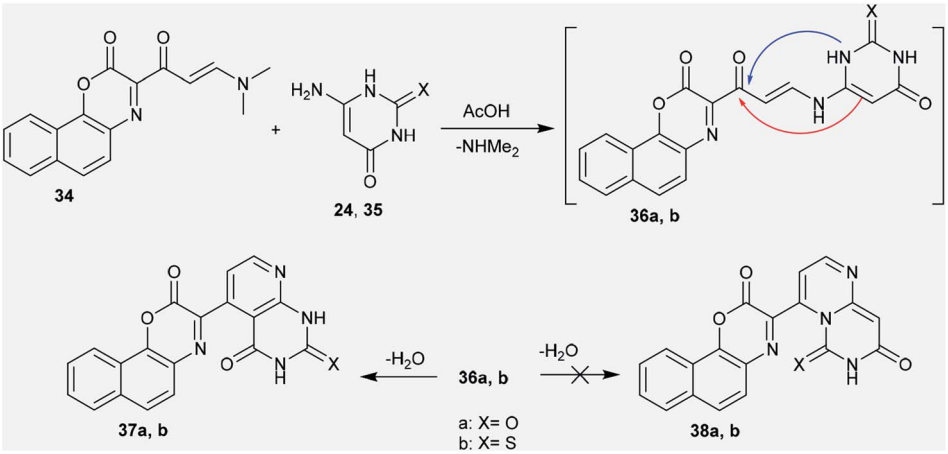
Scheme 8 Synthesis of 9-hydroxy-4*H*-pyrimido[1,6-*a*]pyrimidin-4-one.

acetic acid to afford the respective 2-thioxo(oxo)-4-oxo-pyrido[2,3-*d*]pyrimidines **37a** and **b**, respectively, instead of the formation of 6*H*-pyrimido[1,6-*a*]pyrimidines **38a** and **b**. However, the reactions failed to afford the anticipated dihydro-6*H*-pyrimido[1,6-*a*]pyrimidines **38a** and **b**. A Michael addition-type reaction was proposed for the detection of the formed products (**37a,b**), in which the exocyclic amino group of the amino-pyrimidine attacks the active C=C double bond of enaminone **34**; this resulted in the elimination of a dimethylamine molecule and the generation of the non-isolable intermediates **36a** and **b**. The endocyclic imino group of aminopyrimidine is known to be a stronger nucleophile;[44,45] however, it has high steric hindrance.[46] In this route, the cyclization of the intermediates (**36a,b**) into the desired pyridopyrimidines (**37a,b**) or pyrimidopyrimidines (**38a,b**) could be achieved. The addition of the exocyclic C=C to the carbonyl ketone took place rather than the intramolecular nucleophilic addition of the NH group of the pyrimidinone ring at the carbonyl ketone. However, the formation of the pyridopyrimidines (**37a,b**) was accomplished based on the spectroscopic data of the isolated products (Scheme 9).[47]

2.2.2. Synthesis from 6-aminopyrimidine-2,4-diol. Moreover, the hetryl aldehyde **39** was reacted with 6-aminopyrimidine-2,4-diol (**40**) in an alcoholic solution of potassium hydroxide at reflux temperature to afford 3-hetrylcarbonyl-pyrimidopyrimidine-dione **41**. The mechanism of this reaction is proposed in Scheme 10. An initial nucleophilic attack of the hydroxide ion generated from potassium hydroxide took place at C2 of the chromen-4-one ring, followed by protonation and tautomerization of the carbonyl group at C4. Then, pyranone ring cleavage was accomplished to generate the intermediate **A-2**. In another route, 6-aminopyrimidine-2,4-diol (**40**) was rearranged to the keto-form with generation of the anion by abstraction of the proton at C3 by the action of hydroxide ion with the formation of the intermediate **B-2**, which was tautomerized to the intermediate **C-2**. The interaction of the intermediates **A-2** and **C-2** yielded the respective pyrimido[1,6-*a*]pyrimidine-dione (**41**) through nucleophilic attack of the anion carbon at the carbonyl group of the intermediate **A-1**, followed by the cyclocondensation step.[48]

2.3. Synthesis of pyrimidoquinazolines

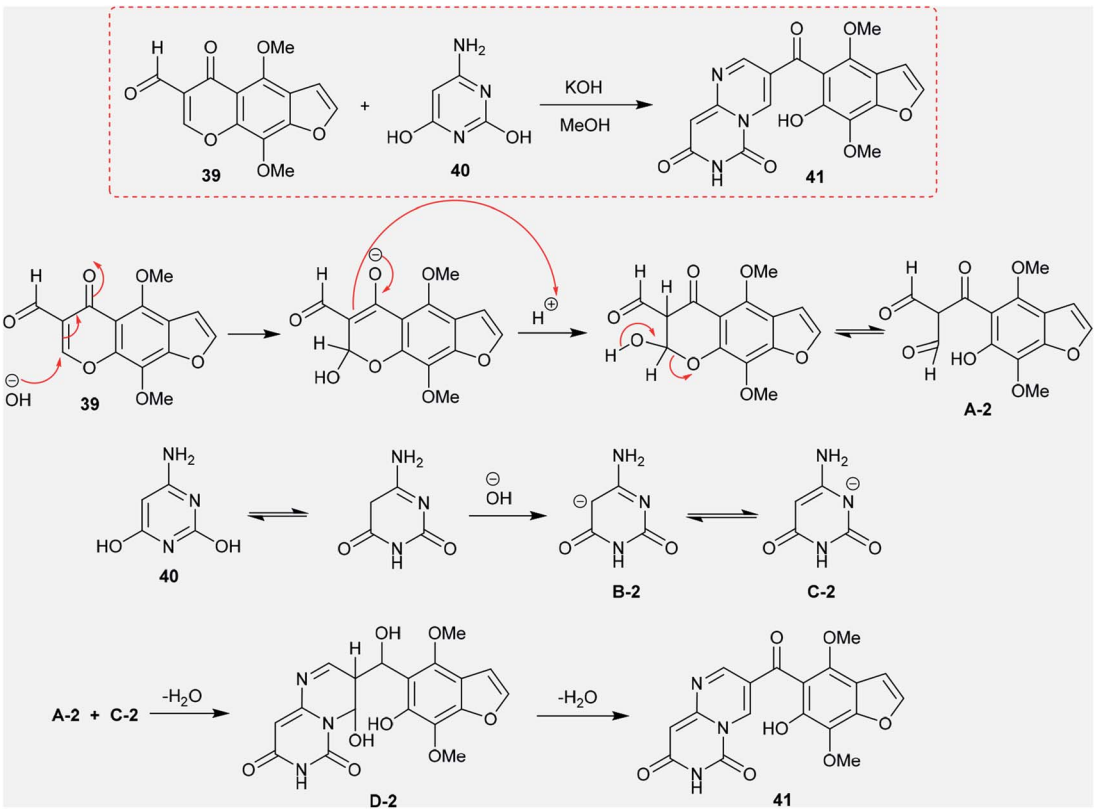
Quinazolinone analogs were reported to have a comprehensive diversity of biological activities and have been widely used and applied in various medical and pharmaceutical fields;[49] they are



Scheme 9 Synthesis of 2-thioxo(oxo)-4-oxo-pyrido[2,3-*d*]pyrimidines.

applied as antioxidant,[50] antihyperlipidemic,[51] antiviral,[52] antitumor,[53] analgesic, anti-inflammatory,[54] anticonvulsant,[55] antihypertensive,[56] and antimicrobial agents.[57]

2.3.1. Synthesis from pyrimidine-2,4(1*H*,3*H*)-dione. Suchy and Hudson[58] reported a simple multi-step synthetic route for the construction of *tert*-butyl 2-(4-bromo-1,10-dioxo-1*H*-pyrimido[6,1-*b*]quinazolin-2(10*H*)-yl)acetate (**46**) *via* an elegant procedure. This process represents the first synthesis of a heterocyclic compound incorporating a 1,10-dioxo-1*H*-pyrimido[6,1-*b*]quinazoline core. Thus, *tert*-butyl acetate **43** was obtained in moderate yield by bromination of uracil (**42**)[59] in the first step, followed by treatment with *t*-butyl bromoacetate in DMF containing K_2CO_3, treatment with phosphorus oxychloride, and subsequent reaction with 1,2,4-triazole in acetonitrile catalyzed by TEA. Heating the respective 1*H*-1,2,4-triazolyl-pyrimidine **43** with anthranilic acid in 1,4-dioxane yielded the aryl cytosine **44**. The reaction proceeded in the presence of 10% water to facilitate the nucleophilic substitution and in the absence of base. The aromatic nucleophilic substitution of **43** with anthranilic acid progressed according to the



Scheme 10 Synthesis of 3-(aroyl)-6*H*-pyrimido[1,6-*a*]pyrimidine-6,8(7*H*)-dione.

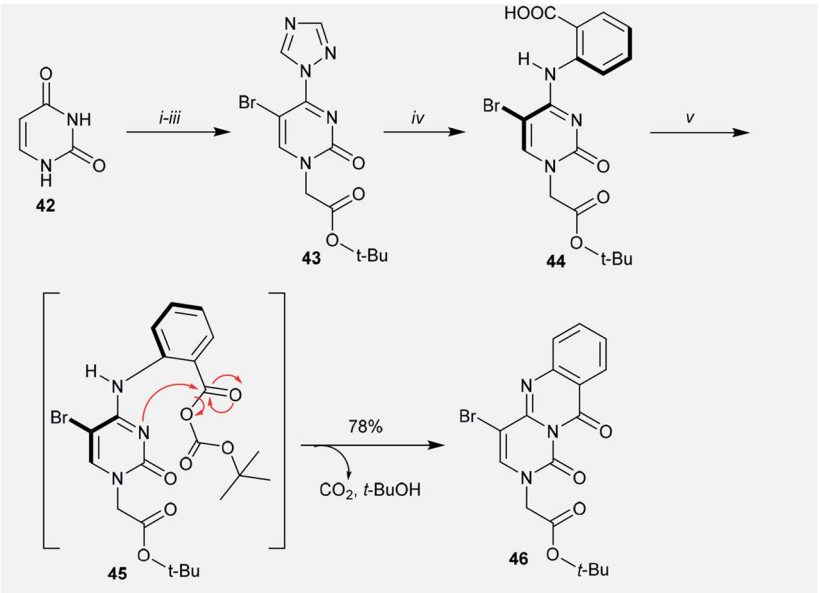
method reported by Pedroso *et al.*[60] Product **43** was obtained after recrystallization in 86% yield. In the last step, *tert*-butyl 2-(4-bromo-1,10-dioxo-1*H*-pyrimido[6,1-*b*]quinazolin-2(10*H*)-yl) acetate (**46**) was synthesized by treatment of aryl cytosine **44** with Boc anhydride or di-*tert*-butyl pyrocarbonate (Boc_2O) in the presence of 4-dimethyl-aminopyridine (DMAP) as a base. The product **46** was formed in 78% yield through *in situ* generation of the intermediate **45**, which followed an intramolecular decarboxylative coupling.[61] The intramolecular nucleophilic attack of the nitrogen atom at position 3 of the cytosine ring on the carbonyl group of the carboxylate fragment proceeded with the elimination of *tert*-butanol and carbon dioxide molecules (Scheme 11).

2.3.2. Synthesis from 4,6-dichloropyrimidine. Proficient multi-step synthetic routes have been investigated by Li *et al.*[62] for the construction of *N*,6-*bis*(aryl)-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imines **54a–l** in good yields (52–80%). Therefore, 4,6-dichloropyrimidine (**47**) reacted with aryl amines **3** in isopropanol catalyzed by hydrochloric acid to afford 6-chloro-*N*-aryl-pyrimidin-4-amines (**49**).[63] Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of **49** with boronic acid **50** yielded the desired *N*,6-diaryl-pyrimidin-4-amines (**51**). Subsequently, condensation of **51** with 4-substituted-benzaldehydes (**52**) afforded the Schiff bases **53**. Cyclization of compounds **53** to the desired pyrimidoquinazolines **54** was accomplished by sodium borohydride treatment in methanol at room temperature. In this sequence, different conditions were applied for these reactions, in which the best yields (**53a**, 70%) of the reactions were obtained using sodium borohydride as an additive in methanol as a solvent at room temperature (Scheme 12).[62]

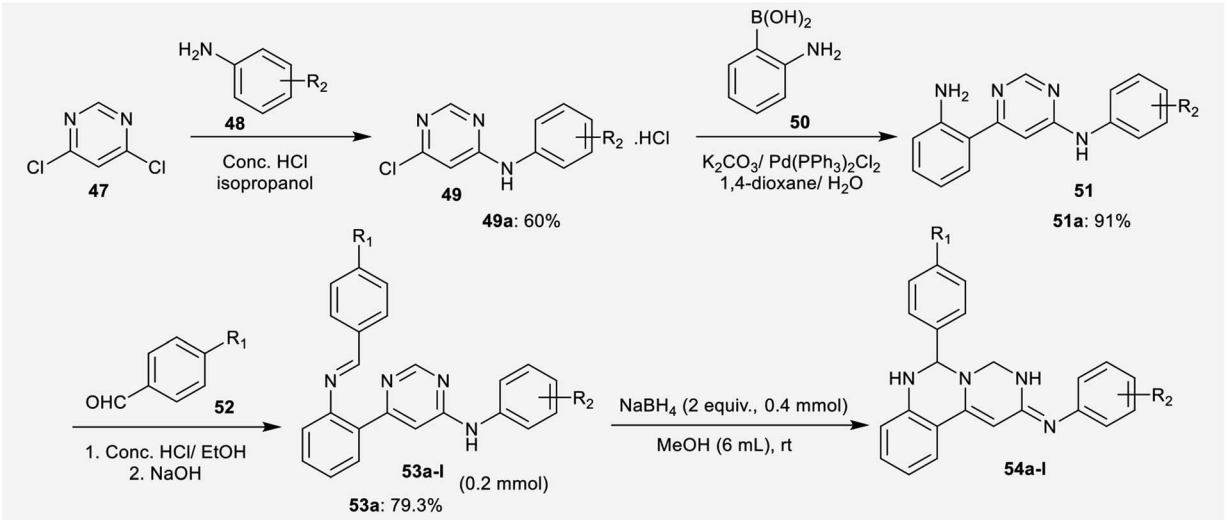
A proposed mechanism for the synthesis of pyrimidoquinazolines **54** is presented in Scheme 13. Accordingly, there are two possible pathways (A and B) for the cyclization step of compounds **53** to afford the pyrimido[1,6-*c*]quinazolines (**54**). In route A,[1,3] proton transfer generates the tautomer **55**. The carbon at position 2 of the pyrimidine ring is attacked by the hydrogen anion produced from sodium borohydride to form the intermediate **56**. The nitrogen anion of **56** enables intramolecular cyclization by attacking the C=N bond to form intermediate **57**. Alcoholysis of the intermediate **57** with methanol yields the target products **54**. In route B, reductive dearomatization of **53** occurs first by the action of sodium borohydride; then, the generated nitrogen anion of the intermediate **58** undergoes alcoholysis to form the intermediate **59**, and finally,[1,3] proton transfer yields the products **54**.[62]

In the same way, pyrimido[1,6-*c*]quinazoline (**61**) was synthesized with a yield of 50% by treatment of *N*-methyl-pyrimidine **60** with $NaBH_4$/MeOH at room temperature. Product **61** was obtained by following pathway B without the step of[1,3] proton transfer (Scheme 14).[62]

2.3.3. Synthesis from methyl *N*-cyano-2-nitrobenzimidates. Yin *et al.*[64] employed a method of tandem condensation for the synthesis of substituted-6-amino-3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolines (**63**) with excellent yields through a two-step synthesis. The products **63** were obtained from the reaction of methyl benzimidates **62** each with 3-chloropropan-1-amine hydrochloride catalyzed by sodium bicarbonate and subsequent reductive cyclization by treatment with an Fe/HCl system. In the first step, two equivalents of chloroalkyl-amines (hydrochloride and sodium bicarbonate) were used; meanwhile, four equivalents of iron and excess potassium carbonate were used

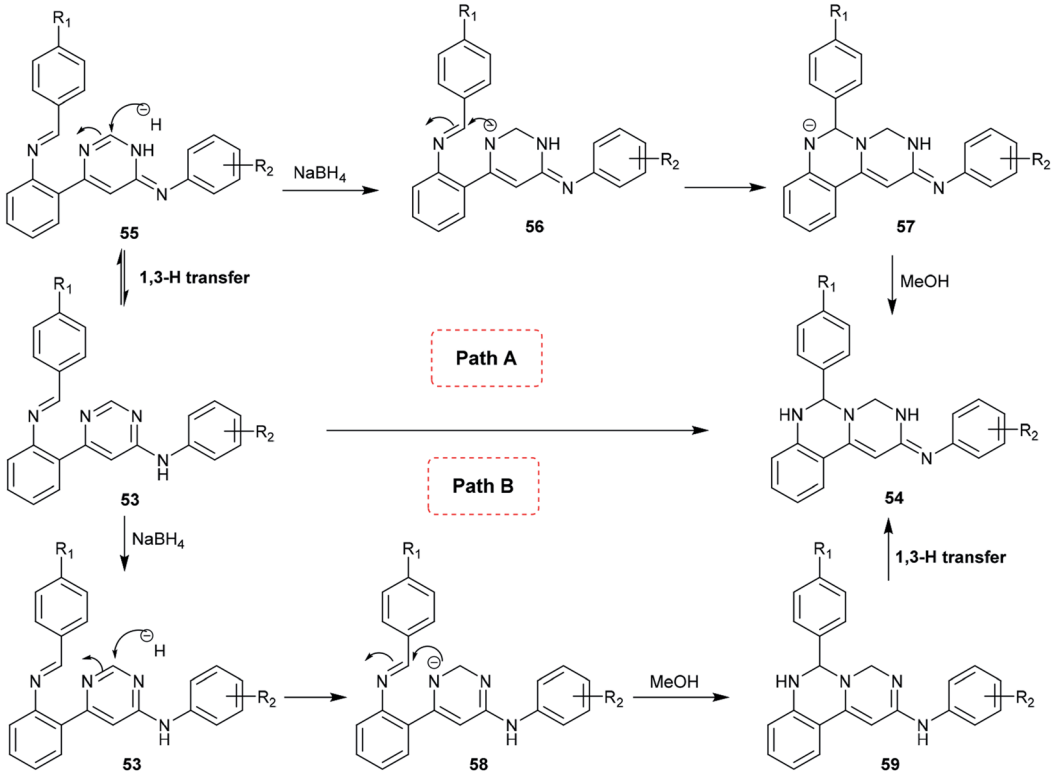


Scheme 11 Synthesis of *tert*-butyl 2-(4-bromo-1,10-dioxo-1*H*-pyrimido[6,1-*b*]quinazolin-2(10*H*)-yl)acetate.

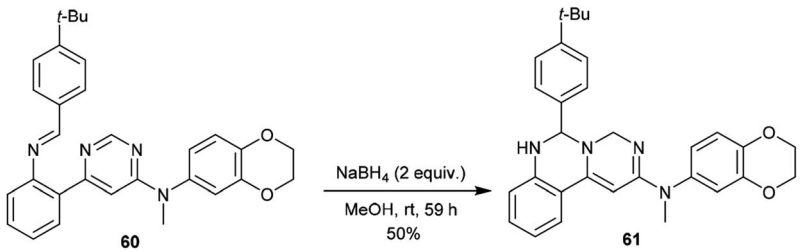


Product 54	R_1	R_2	Yield %	Product 54	R_1	R_2	Yield %
a	CF_3	3-OCH_2CH_2O-4	70	g	OMe	3-OCH_2CH_2O-4	57
b	CO_2Me	3-OCH_2CH_2O-4	54	h	H	4-CF_3	58
c	Br	3-OCH_2CH_2O-4	72	i	H	4-Br	71
d	H	3-OCH_2CH_2O-4	79	j	H	H	71
e	Me	3-OCH_2CH_2O-4	52	k	H	4-Me	66
f	*t*-Butyl	3-OCH_2CH_2O-4	52	l	H	4-OMe	80

Scheme 12 Synthesis of *N*,6-*bis*(aryl)-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imines.



Scheme 13 Proposed mechanism for the synthesis of 2*H*-pyrimidoquinazolines **54**.



Scheme 14 Synthesis of *N*-methyl-6,7-dihydro-4*H*-pyrimido[1,6-*c*]quinazoline.

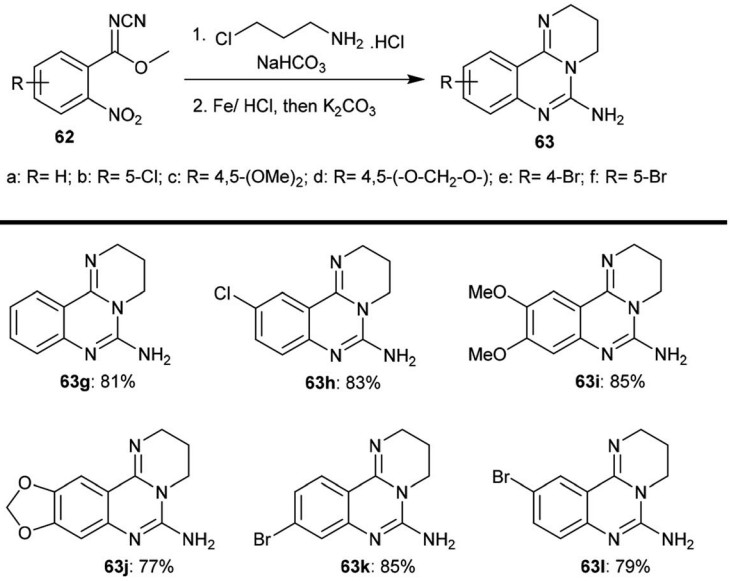
in the next step, which involved processing by refluxing the reactants in an Fe–HCl system for three hours and subsequent addition of potassium carbonate with refluxing for an additional six hours. The procedure involved a one-pot sequence of intramolecular *N*-alkylation (Scheme 15).

2.3.4. Synthesis from pyrimidine-dione. Heating of substituted isotonic anhydrides (**64a–e**) with 6-methylpyrimidine-2,4(1*H*,3*H*)-dione (**65**) in xylene afforded the respective 1*H*-pyrimido[6,1-*b*]quinazoline-1,10(4*H*)-diones **66a–e**, respectively. The products were formed through ring-opening of the respective anhydride with condensation and subsequent ring closure (Scheme 16).[65]

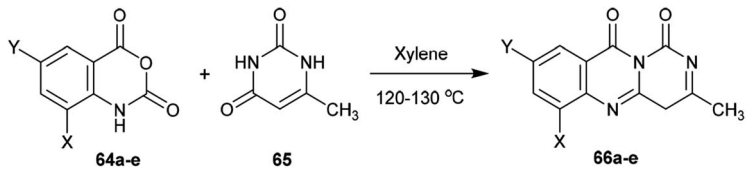
2.3.5. Synthesis from quinazolinones. Treatment of 2-methylquinazolin-4(3*H*)-one (**67**) with phosphorus pentasulfide and phosphorus oxychloride followed by reaction with thiourea in ethanol at reflux temperature yielded 2-methylquinazoline-4-thiol (**68**). The respective 2-substituted-quinazoline-4-thiol derivatives (**69a–d**) were synthesized by reactions of **68** with aryl aldehydes. Solvent-free reactions of **69a–d** with esters of amino acids catalyzed by TEA at their reflux temperatures yielded the corresponding 6-substituted-2,3-dihydro-4*H*-pyrimidoquinazolinones **70a–d** in respectable yields (79–87%). The use of solvents and basic catalysts in the previous reactions reduces the yield of the products. The products **70a–d** were obtained by reactions involving nucleophilic substitution and thermal cyclization processes.[66] Otherwise, Špirková and Stankovský[67] reported the synthesis of pyrimidoquinazolinones **71** by heating 2-phenyl-quinazoline-4(3*H*)-thiones (**68a–c**) with equimolar amounts of methyl esters of glycine, α-alanine or β-alanine in an oil bath in the absence of basic catalyst (Scheme 17).

Congruently, chlorination of 6-bromo-2-substituted-quinazolin-4(3*H*)-ones **72a,b** with phosphorus oxychloride yielded the corresponding chlorinated products **73a,b**, respectively, in which the chlorination occurred at C4 of the quinazolin-4(3*H*)-one ring. Accordingly, cyclization step reactions of **73a** and **73b** with 2-amino-5-bromobenzoic acid, respectively, were performed by heating in butanol at its reflux temperature to afford 2,10-dibromo-6-substituted-8*H*-quinazolinoquinazolinones **74a** and **74b**. The products were acquired by nucleophilic attack of the amino group at C4 of the quinazoline ring with chlorine atom substitution. Subsequent[1,3] H transfer and intramolecular cyclocondensation yielded the respective products **74a** and **74b** (Scheme 18).[68]

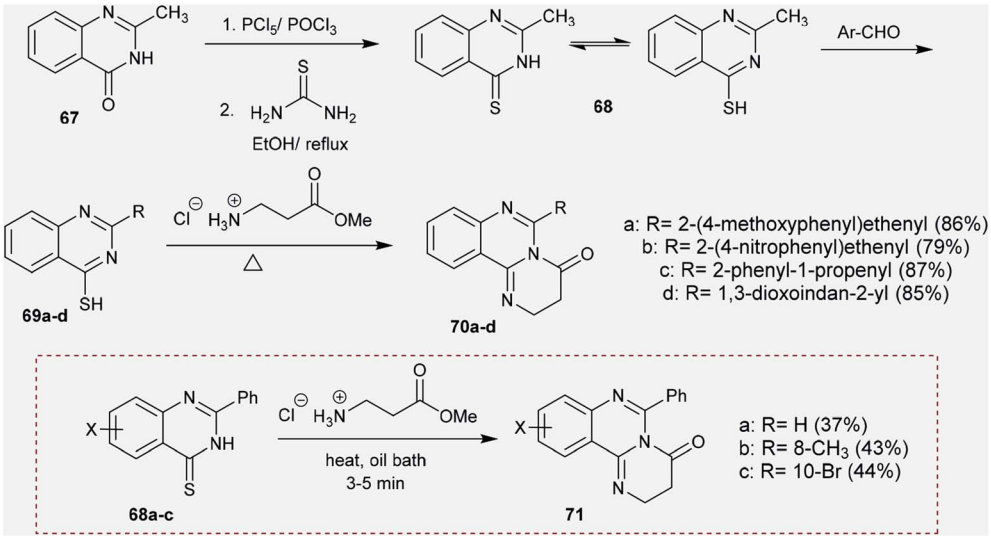
2.3.6. Synthesis from aryl aldehydes. An unpretentious method was conveyed for the synthesis of ethyl pyrano-pyrimido



Scheme 15 Synthesis of 3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolines.



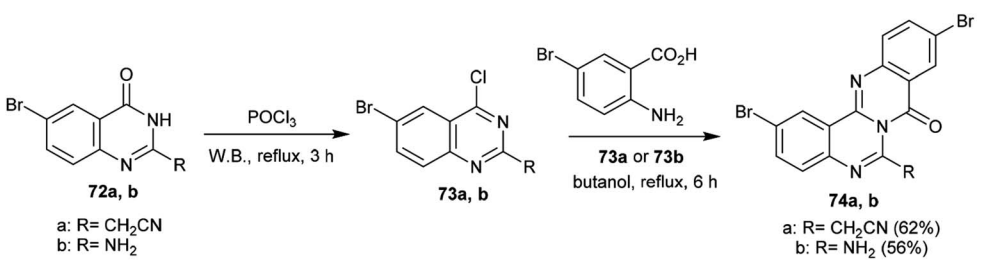
Scheme 16 Synthesis of 3-methyl-1*H*-pyrimido[6,1-*b*]quinazoline-1,10(4*H*)-diones.



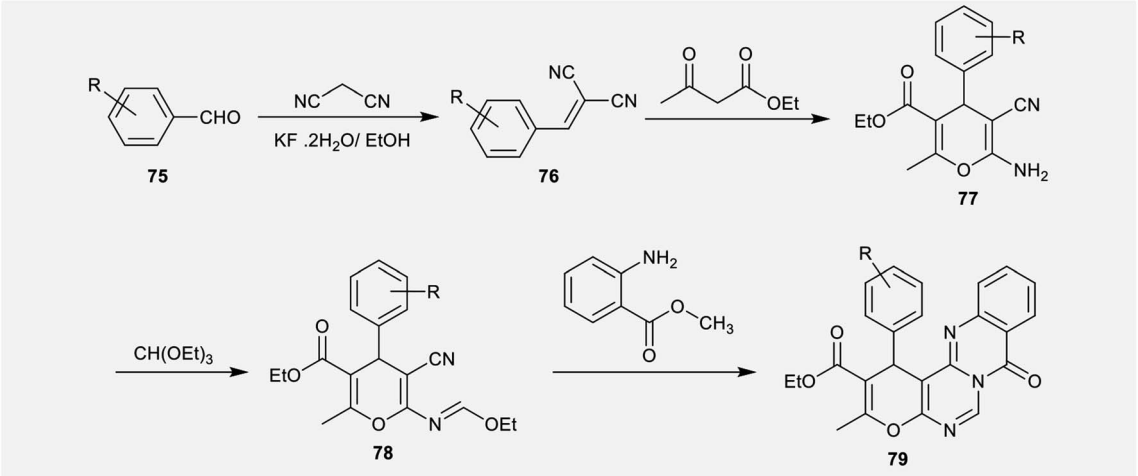
Scheme 17 Synthesis of 6-substituted-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones.

[6,1-*b*]quinazoline-2-carboxylates (**79**) by Shi *et al.*[69] through multi-step reactions. Consequently, condensation of aryl aldehydes **75** with malononitrile yielded the arylidene malononitriles **76** according to the procedure reported by Venkateswarlu *et al.*[70] Arylidenes **76** were reacted with ethyl 3-oxobutanoate to afford the desired ethyl carboxylates **77**. Refluxing of ethyl carboxylates **77** with triethyl orthoformate in acetic anhydride yielded the ethoxymethylene-amino analogs **78**. The cyclization of **78** with methyl 2-aminobenzoate in acetic acid at reflux temperature yielded the corresponding ethyl pyrano-pyrimido [6,1-*b*]quinazoline-2-carboxylates (**79**) with yields ranging from 65% to 71%. The cyclization step followed an initial nucleophilic attack of the arylamino function of methyl 2-aminobenzoate at the ethoxymethylene carbon with the elimination of an ethanol molecule and subsequent intramolecular nucleophilic attack at the nitrile function to generate an imino group, which attacked the ester group to afford the target products **79** (Scheme 19).[69]

2.3.7. Synthesis of quaternary salts. A proficient procedure for the synthesis of tetrahydropyrimido[1,2-*c*]quinazolin-5-ium salts (**84**) was conveyed by Stankovský and Filip.[71] Accordingly, heating of amidinoyl isothiocyanates (**80**) in benzene yielded the corresponding 2-(disubstituted-amino)-6-substituted-quinazoline-4(3*H*)-thiones (**81**) in quantitative yields. The substitution of the SH group "generated from enolization of the carbothioamide group" with the terminal amino group of 3-aminopropan-1-ol was achieved by heating the reactants to afford the respective 4-(3-hydroxypropylamino)quinazolines **82a,b**. Subsequent heating of **82a,b** with hydrochloric acid yielded the corresponding pyrimidoquinazolinium chlorides **83a,b**, respectively. The structures of **83a,b** have two other possible tautomeric



Scheme 18 Synthesis of 2,10-dibromo-6-substituted-8*H*-quinazolinoquinazolinones **74**.



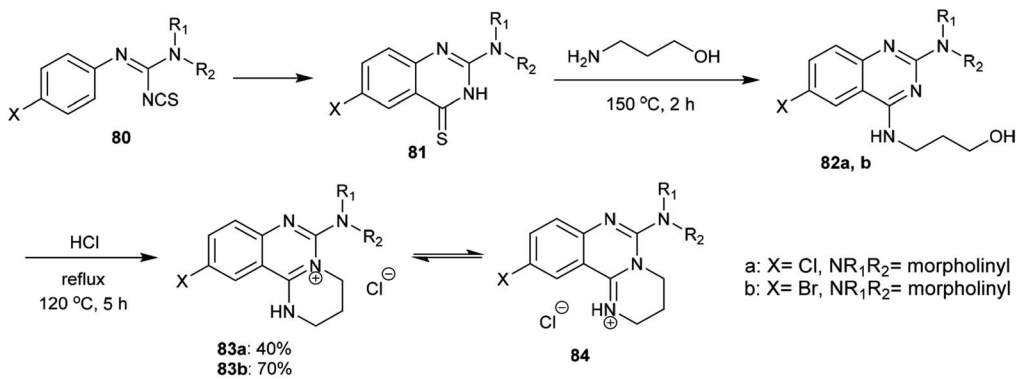
Product 79	R	Yield %	Product 79	R	Yield %
a	4-OCH_3	71	e	2-Cl	65
b	3,4-$(OCH_3)_2$	68	f	4-Cl	66
c	4-CH_3	70	g	H	70
d	2,4-Cl_2	67	h	3-NO_2	65

Scheme 19 Synthesis of ethyl 8-oxo-1*H*,8*H*-pyrano-pyrimido[6,1-*b*]quinazoline-2-carboxylate.

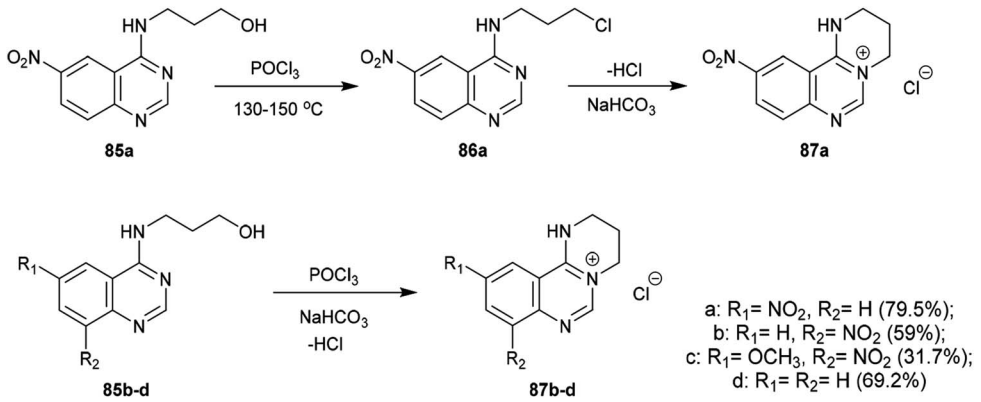
structures, identified as pyrimidoquinazolinium chlorides **84** (Scheme 20).

An efficacious method for the synthesis of quaternary salts was conveyed by Yoshikawa and Shitago[72] involving intramolecular cyclization reactions of the anticipated 4-amino-hydroxy-propane-6,8-disubstituted-quinazolines **86**. As a result, the treatment of 4-amino-6,8-disubstituted-quinazolines **85a–d** with phosphorus oxychloride at reflux temperature yielded the desired chlorinated products **86**, which were cyclized to the tetrahydropyrimido[1,2-*c*] quinazolin-5-ium chlorides **87a–d** by treatment with sodium bicarbonate. The mechanism of this cyclization followed an initial[1,3] proton transfer of the proton of the imine group followed by elimination of the HCl molecule (Scheme 21).

2.3.8. Synthesis from quaternary salts. Treatment of tetrahydropyrimido[1,2-*c*]quinazolin-5-ium chlorides **87a–d** with 10% sodium hydroxide solution yielded the free bases of pyrimido[1,2-*c*]quinazolines **88a–d** in moderate to good yields (31.7–79.5%). The products were formed by the dehydration of the generated intermediate **A-3**. On the other hand, treatment of 3-((6-nitroquinazolin-4-yl)amino)propan-1-ol (**85a**) with conc. sulfuric acid and sodium nitrite and subsequent heating with sodium hydroxide solution yielded pyrimidoquinazoline **88a** through two possible mechanistic routes. Nitrosation of the imine group with nitrosyl sulfate and sulfonation of the terminal hydroxy group activated the cyclization by abstraction of the nitroso group and subsequent substitution of the hydrogen sulfate group of the intermediate **A-3**. Alternatively, the cyclization step proceeded with the elimination of



Scheme 20 Synthesis of pyrimidoquinazolinium chlorides **84**.

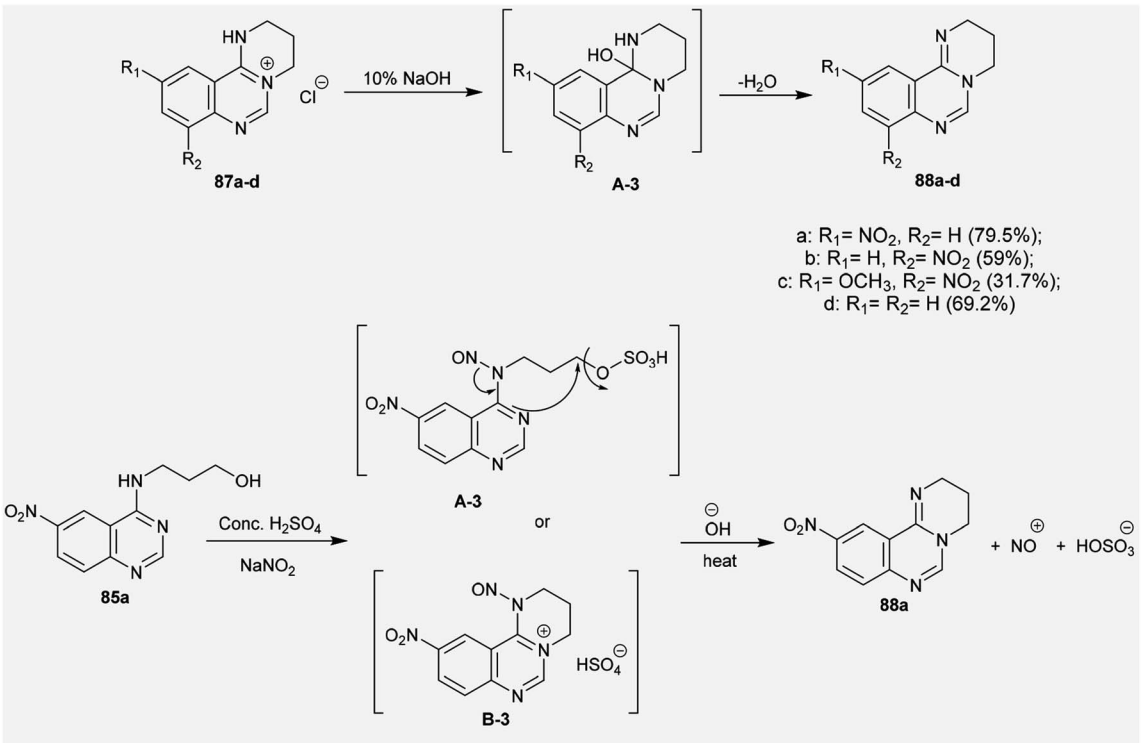


Scheme 21 Synthesis of pyrimidoquinazolinium chlorides.

a hydrogen sulfate group to generate the tetrahydropyrimido [1,2-*c*]quinazolin-5-ium hydrogen sulfate, intermediate **B-3** (Scheme 22).[72]

2.4. Synthesis of tricyclic systems

2.4.1. Synthesis of cycloalka-pyrimido[1,6-*a*]pyrimidinones. From the literature viewpoint, the construction of the pyrimido[4,5-*d*]pyrimidine heterocyclic system has been achieved through multistep synthetic routes.[73,74] Moreover, Hussein and coworkers[41,75] reported an unpretentious method for the construction of 1-thioxo-1,2,8,9-tetrahydro-cycloalkyl-pyrimido-pyrimidinones **92a–d**. Therefore, condensation of the sodium salts of formyl cyclic ketones (**89**) with 6-aminothiouracil in piperidine acetate/acetic acid systems at reflux temperature afforded the cyclocondensation products **92a–d** in noteworthy yields. The reactions progressed by nucleophilic addition of the amino group of 6-aminothiouracil to the aldehydic carbonyl group of **90b** (*in situ* generated from the hydrolysis of sodium salts **89** with water) in piperidine acetate to generate the intermediates **91**. The tricyclic systems, cycloalkyl-pyrimidopyrimidinones **92a–d**, have three possible tautomeric structures, **A–C**. The nitrogen atom at position 2 of the pyrimidopyrimidine ring has a hydrogen atom, which enables the enolization of the amidic carbonyl group at position 3 of the ring, and thione-thiol tautomerization at position 1 forms the possible structures **A–C**.[41] Intramolecular



Scheme 22 Synthesis of 8,10-disubstituted-3,4-dihydro-2*H*-pyrimidoquinazolines.

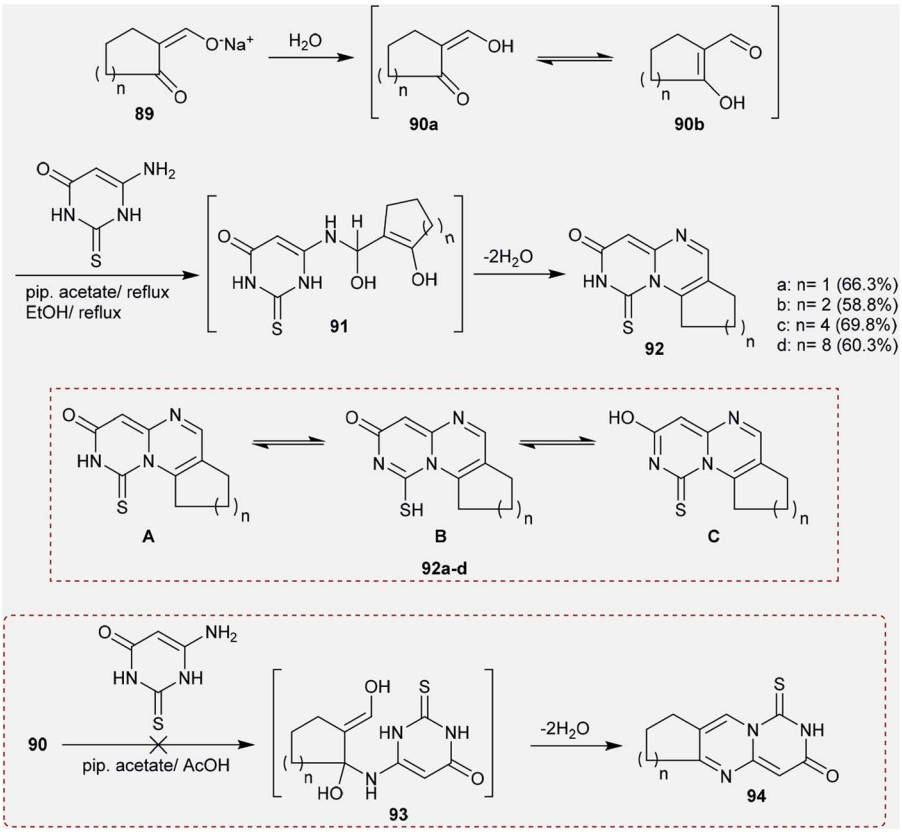
cyclocondensation of the intermediates **91** yielded the respective pyrimidopyrimidines **92a–d** instead of generating the planned products **94**[76–78] (Scheme 23).

2.4.2. Synthesis of pyrazolo-pyrimido[1,2-*c*]pyrimidines. To construct the pyrimidopyrimidine ring, an efficient multi-step synthetic route was applied by Karoui *et al.*[79] by succeeding acid-catalyzed condensation reactions. Consequently, the reactions of 2-(substituted-(ethoxy)methylene)malononitriles **95** with phenylhydrazine yielded the respective 4-cyano-5-amino-3-substituted-1-phenyl-1*H*-pyrazoles **96**. The imino group of phenyl-hydrazine performed a nucleophilic attack at the nitrile function of malononitriles **95**. Subsequent treatment of pyrazoles **96** with triethylorthoformates in acetic acid as a catalyst at reflux temperature yielded the desired ethyl carbonoimidates **97**.[80,81] The ethyl carbonoimidates **97** were further treated with ammonia in ethanol containing a catalytic amount of acetic acid at reflux temperature to afford the respective 3,6-disubstituted-4-amino-1-phenyl-1*H*-pyrazolopyrimidines **98**.[82] Afterwards, pyrazolopyrimidines **98** were reacted with 2,3-disubstituted-3-ethoxyacrylonitriles in ethanol catalyzed by acetic acid to afford the anticipated tricyclic iminopyrazolo[4,3-*e*]pyrimido[1,2-*c*]pyrimidines **99** (Scheme 24).[79]

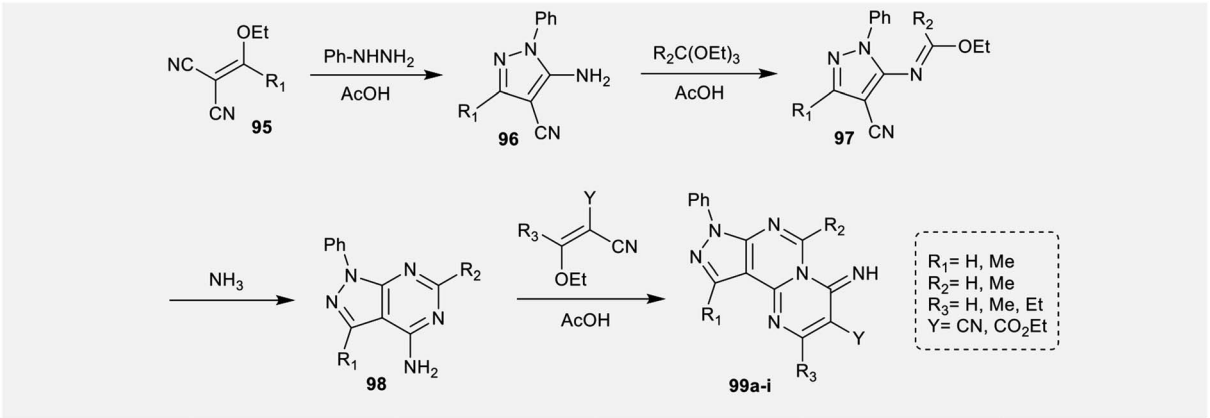
2.4.3. Synthesis of pyrimidopurine-diones. Treatment of 5,6-diamino-3-substituted-pyrimidine-2,4(1*H*,3*H*)-diones **100a** and **100b** each with cycloalkyl carboxylic acids or benzoic acid in methanol catalyzed by EDC yielded the corresponding amides **101a–e**.[83] Alternatively, the amides **101a–e** reacted with 1,3-dibromopropane in DMF/K_2CO_3 to afford pyrimidopyrimidindiones **102a–e**, respectively, with yields of 42–63%. The high reactivity of 1,3-dibromopropane allowed the reaction between the nitrogen atom at position 1 and the amino group attached to position 6 of the uracil. Further refluxing of **102a–e** with HMDS at reflux temperature for 18 h yielded the tricyclic systems **103a–e**, respectively, with yields of 38–74%. An alternative route for the synthesis of a xanthine tricyclic system was reported through the preparation of compound **103a**. Therefore, the reaction of **100a** with benzaldehyde in ethanol at reflux temperature yielded compound **104a**.[84] The bicyclic **105a** was synthesized in a yield of 54% by the reaction of 1,3-dibromopropane with **104a** in a DMF/K_2CO_3 system. Ring closure of compound **105a** was accomplished by an oxidative step by reaction with thionyl chloride to yield xanthine product **103a** in 87% yield (Scheme 25).[85] The substituents of 2-(3-noradamantyl)-, such as 2-(adamantan-1-yl)-9-propyl-5,6-dihydro-4*H*,8*H*-pyrimidopurine-dione (**102**), have been verified to be selective antagonists for adenosine A1 receptor.[86,87]

2.5. Synthesis of tetracyclic systems

A simple multi-step synthetic method was reported by Abdel-Hafez *et al.*[88] for the preparation of a tetracyclic system incorporating the pyrimido[1,2-*c*]pyrimidine scaffold. Thus, 3-amino-4,6-dimethyl-selenopheno[2,3-*b*]pyridine-2-carbonitrile (**107**)



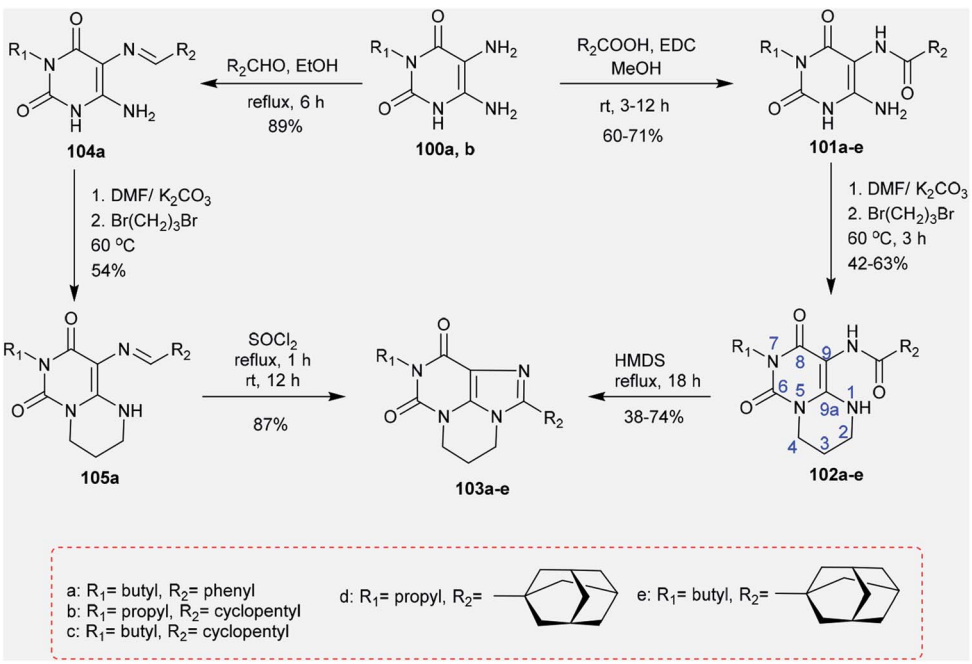
Scheme 23 Synthesis of 1-thioxo-1,2,8,9-tetrahydro-cycloalkyl-pyrimidopyrimidinones.



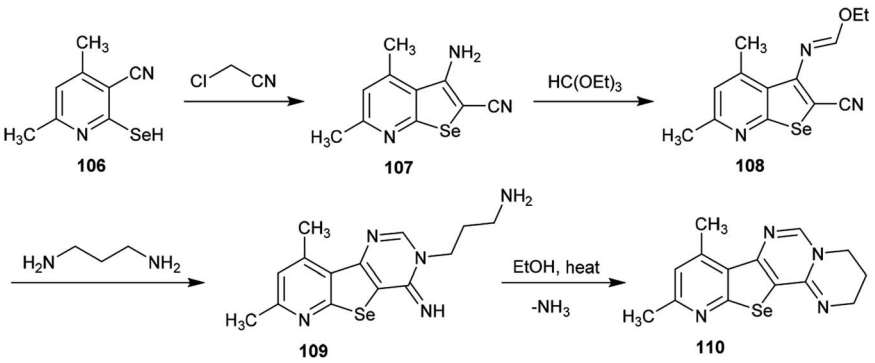
Product 99	R_1	R_2	R_3	Y	Yield %
a	CH_3	H	H	CN	68
b	CH_3	H	CH_3	CN	54
c	H	CH_3	H	CN	71
d	H	H	H	CN	77
e	H	H	Et	CN	70
f	CH_3	H	CH_3	CO_2Et	71
g	CH_3	H	Et	CO_2Et	69
h	H	H	H	CO_2Et	89
i	H	H	CH_3	CO_2Et	78

Scheme 24 Synthesis of 2,3,6,10-tetrasubstituted-8-phenylpyrazolopyrimidopyrimidin-4(8*H*)-imines.

was prepared by reaction of 2-hydroseleno-4,6-dimethylnicotinonitrile (**106**) with 2-chloroacetonitrile.[89] The reaction of selenopheno[2,3-*b*]pyridine **107** with triethyl orthoformate yielded the respective ethyl formimidate **108**, which was treated with propane-1,3-diamine in 1,4-dioxane at room temperature to afford the tricyclic pyrido-selenopheno[3,2-*d*]pyrimidine **109**. The intramolecular cyclization of compound **109** to the target product **110** was accomplished by heating in ethanol. In this cyclization, the terminal amino group of the propyl chain acts as a nucleophile which attacks the C=NH at position 4 of the pyrimidine ring, resulting in the elimination of an ammonia molecule (Scheme 26).[88]



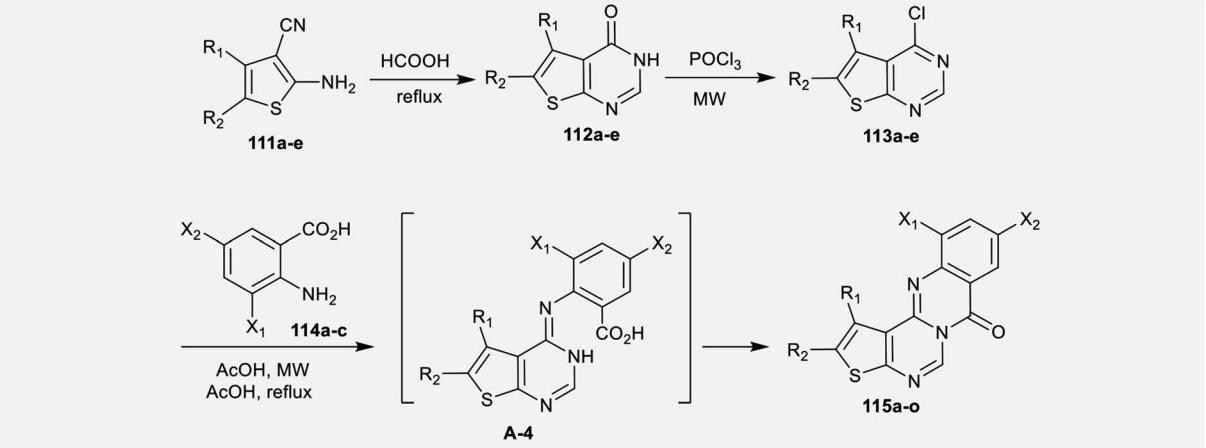
Scheme 25 Synthesis of pyrimidopurine-diones.



Scheme 26 Synthesis of pyrido-selenopheno[2,3-*e*]pyrimidopyrimidine.

The reaction of enaminonitriles of thiophenes **111a–e** with formic acid at reflux temperature yielded thienopyrimidinones **112a–e**, respectively.[90] Further treatment of **112a–e** with phosphorus oxychloride under microwave irradiation conditions yielded the anticipated chlorinated thienopyrimidines **113a–e**. A series of 7*H*-thienopyrimidoquinazolinones **115a–o** was synthesized by Niementowski reactions[91] of **3a–e** with anthranilic acids **114a–c** under microwave irradiation or reflux[92–95] conditions. The products **115a–o** were formed through nucleophilic attack of the amino group of the anthranilic acids at C4 of thieno[2,3-*d*] pyrimidines **113a–e**, followed by[1,3] proton transfer and subsequent intramolecular cyclocondensation (Scheme 27).[96]

As well, pyridopyrimidinones **117a–g** were synthesized by refluxing 2-amino-nicotinonitriles **116a–g** in formic acid. Niementowski condensation of **117a–g** with anthranilic acids **118a–c** under microwave irradiation conditions, by refluxing in the



Product 115	R_1, R_2	X_1	X_2	Yield % Method A	Yield % Method B
a	-$(CH_2)_4$	H	H	60	95
b	4-Cl-Ph, H	H	H	70	80
c	4-CH_3-Ph, H	H	H	65	85
d	4-OCH_3-Ph, H	H	H	70	85
e	CH_3	H	H	60	80
f	-$(CH_2)_4$	Br	Br	60	90
g	4-Cl-Ph, H	Br	Br	65	95
h	4-CH_3-Ph, H	Br	Br	70	90
i	4-OCH_3-Ph, H	Br	Br	70	85
j	CH_3	Br	Br	60	80
k	-$(CH_2)_4$	H	Br	70	95
l	4-Cl-Ph, H	H	Br	60	85
m	4-CH_3-Ph, H	H	Br	70	90
n	4-OCH_3-Ph, H	H	Br	75	85
o	CH_3	H	Br	60	80

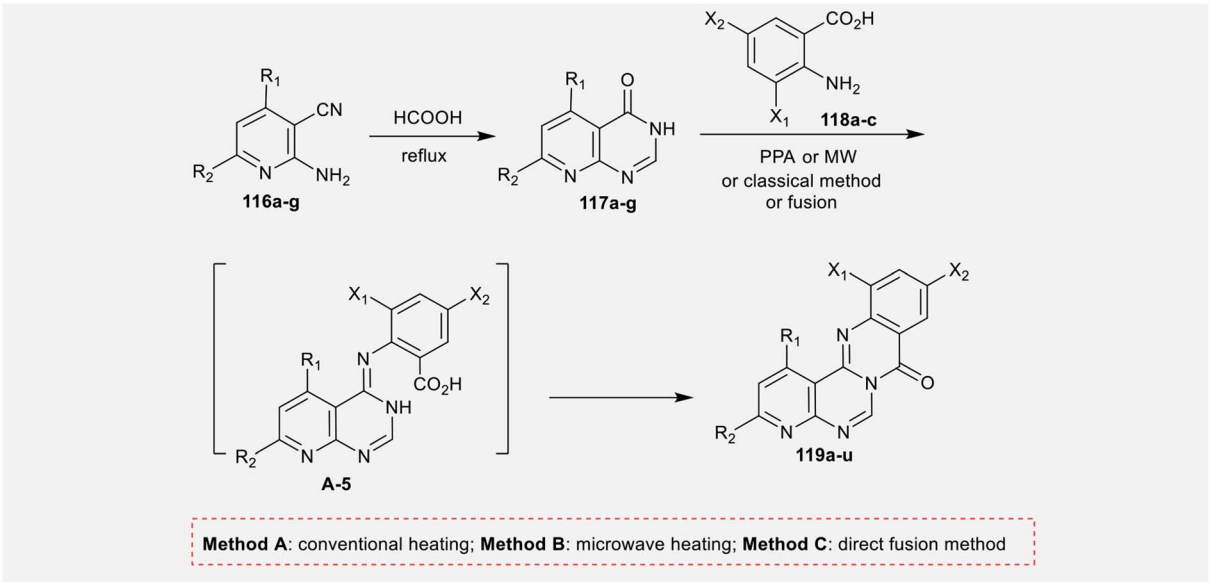
Scheme 27 Synthesis of 7*H*-thienopyrimidoquinazolinones **115**.

presence of polyphosphoric acid, or by the direct fusion method yielded the anticipated 8*H*-pyridopyrimidoquinazolinones **119a–u**. The products **119a–u** were formed through initial condensation between the amino group of the anthranilic acid and the carbonyl group of the pyrimidine ring and a subsequent intramolecular cyclocondensation step of the generated intermediate **A-5** (Scheme 28).[92]

Treatment of Visnagen **120a** (R = H) and Khellin **120b** (R = OCH_3), respectively, in an aqueous solution of potassium hydroxide generated the respective 5-acetyl-6-hydroxy-4-methoxybenzofuran derivatives **121a** and **121b**, which were condensed with dihydropyrimidinone **24** in DMF at reflux temperature to yield 3*H*-furopyrimidoquinazolinones **123a** and **123b**. The reactions of benzofuran derivatives **121a** and **121b** with dihydropyrimidinone **24** produced compounds **122a** and **122b** after a short time; these were condensed in DMF to afford the target compounds **123a** and **123b**, respectively. In the first step, nucleophilic attack of the amino group of dihydropyrimidinone **24** took place at the acetyl carbonyl group of benzofuran derivatives **121a** and **121b**, and subsequent intramolecular cyclocondensation afforded compounds **123a** and **123b**[97] (Scheme 29).

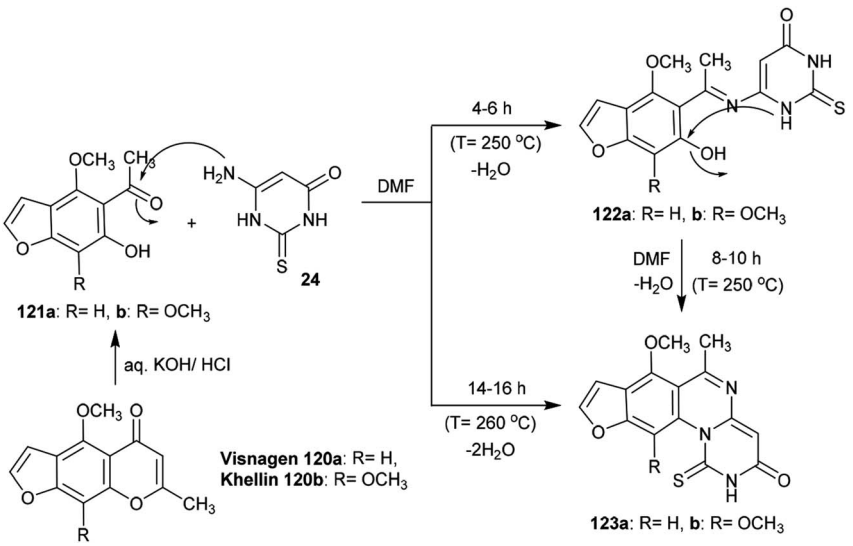
2.6. Synthesis of binary heterocycles

Abu-Hashem and Youssef[98] reported a proficient procedure for the synthesis of 2*H*-pyrimido[1,6-*a*]pyrimidines **129a–d** through



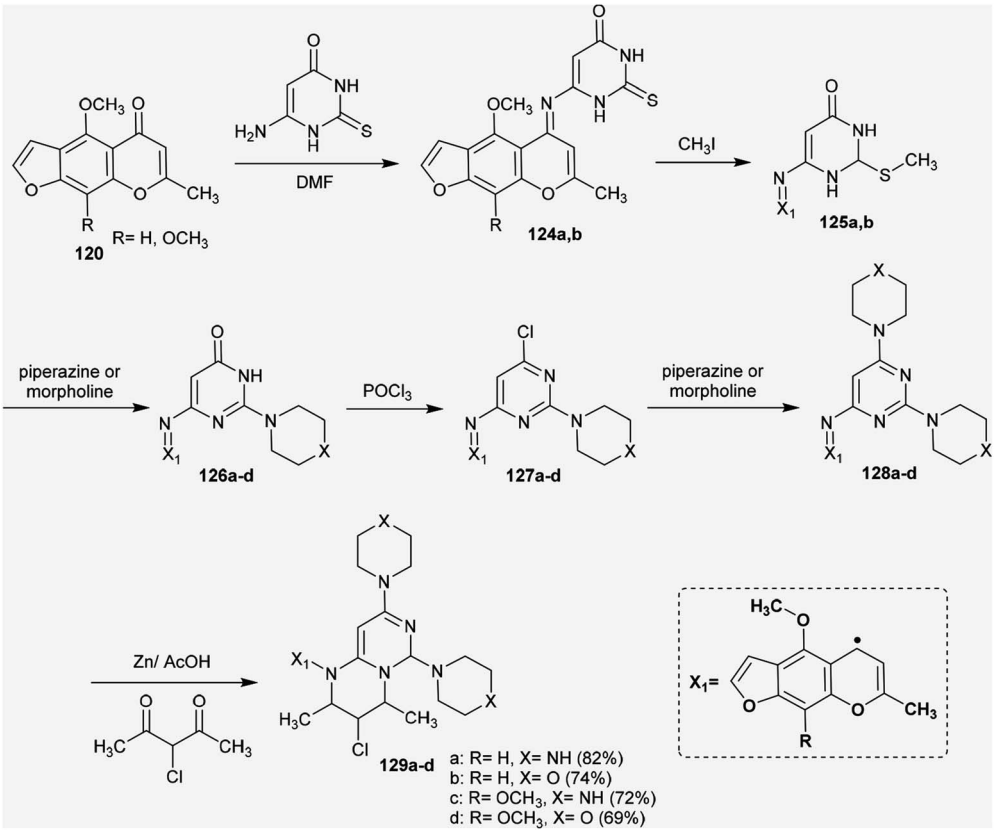
Product 115	R_1	R_2	X_1	X_2	Yield % Method A	Yield % Method B	Yield % Method C
a	2-furfuryl	4-CH_3-Ph	H	H	70	85	20
b	4-OCH_3-Ph	Ph	H	H	75	90	25
c	Ph	4-Cl-Ph	H	H	65	85	30
d	3-NO_2-Ph	4-OCH_3-Ph	H	H	68	90	25
e	4-NO_2-Ph	4-NO_2-Ph	H	H	75	95	30
f	4-CH_3-Ph	Ph	H	H	70	90	20
g	4-Cl-Ph	4-CH_3-Ph	H	H	62	80	20
h	2-furfuryl	4-CH_3-Ph	Br	Br	60	85	--
i	4-OCH_3-Ph	Ph	Br	Br	65	80	20
j	Ph	4-Cl-Ph	Br	Br	68	85	30
k	3-NO_2-Ph	4-OCH_3-Ph	Br	Br	60	80	35
l	4-NO_2-Ph	4-NO_2-Ph	Br	Br	65	80	--
m	4-CH_3-Ph	Ph	Br	Br	68	78	20
n	4-Cl-Ph	4-CH_3-Ph	Br	Br	70	85	25
o	2-furfuryl	4-CH_3-Ph	Br	Br	70	80	20
p	4-OCH_3-Ph	Ph	Br	Br	72	85	20
q	Ph	4-Cl-Ph	H	Br	70	80	--
r	3-NO_2-Ph	4-OCH_3-Ph	H	Br	68	80	--
s	4-NO_2-Ph	4-NO_2-Ph	H	Br	60	75	--
t	4-CH_3-Ph	Ph	H	Br	70	90	20
u	4-Cl-Ph	4-CH_3-Ph	H	Br	75	90	20

Scheme 28 Synthesis of 8*H*-pyridopyrimidoquinazolinones **119**.

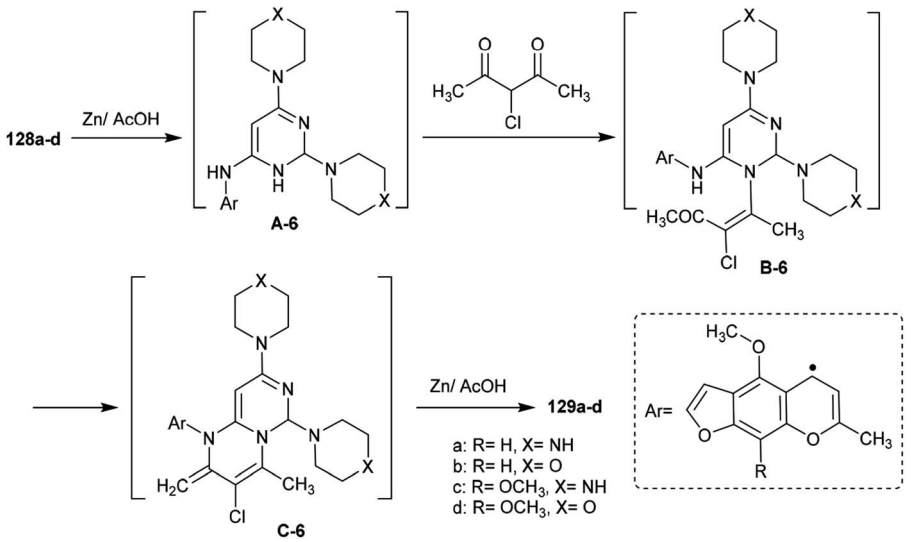


Scheme 29 Synthesis of furopyrimidoquinazolinones.

multi-step reactions. Firstly, condensation reactions of Visnagen and Khellin **120** in refluxing DMF with 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one afforded the Schiff bases **124a** and **b**, respectively. Succeeding methylation of the thione group of **124a** and **b** with methyl iodide afforded the corresponding methylmercaptan analogs **125a** and **b**, which followed nucleophilic substitution by reactions with piperazine and morpholine to yield a series of pyrimidinones **126a–d.** Chlorination of the ketone group at C4 of the pyrimidine ring of **126a–d** was accomplished by reaction with phosphorus oxychloride in dry 1,4-dioxane to afford the anticipated chlorinated products **127a–d.** Consequent halogen substitution of the formed



Scheme 30 Synthesis of tetrahydro-2*H*-pyrimidopyrimidines.



Scheme 31 The proposed ring construction of the pyrimidopyrimidines.

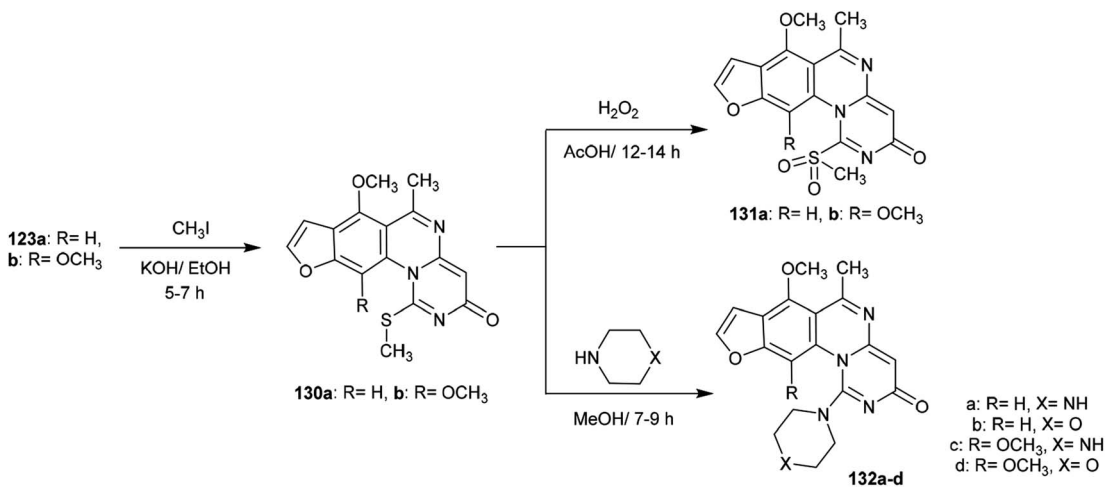
products **127a–d** was achieved by reactions with piperazine and morpholine through nucleophilic attack of the cyclic amine at the chlorine atom at C4 of the pyrimidine ring to afford the trisubstituted pyrimidines **128a–d**, respectively. Lastly, the cyclization step of **128a–d** proceeded by cyclocondensation with 3-chloropentane-2,4-dione in acetic acid containing zinc dust to afford the corresponding 2*H*-pyrimidopyrimidines **129a–d** in good yields (69–82%) (Scheme 30).

The mechanism of the cyclization of the trisubstituted pyrimidines **128a–d** to the respective tetrahydro-2*H*-pyrimido [1,6-*a*]pyrimidines **129a–d** is illustrated in Scheme 31. The initial step in the reactions of pyrimidines **128a–d** with 3-chloropentane-2,4-dione is the reduction of the pyrimidine ring and the substituted imine at C6 of the ring with Zn in acetic acid to generate the intermediate **A-6.** Condensation of the intermediate **A-6** with 3-chloropentane-2,4-dione, which was tautomerized to the enol form, produced the intermediate **B-6;** subsequent intramolecular cyclization after rearrangement of another ketonic carbon to the enol form and condensation with the imine group at C6 of the pyrimidine ring generated the intermediate **C-6.** Subsequent reduction of the intermediate **C-6** with zinc yielded a series of pyrimidopyrimidines **129a–d.**[98]

3. Reactions

3.1. Reactivity of the thione group

Methylation of the thione groups of 3*H*-furopyrimidoquinazolinones **123a** and **123b** with methyl iodide in alcoholic potassium hydroxide solution yielded the methylmercaptan derivatives **130a** and **130b**, respectively. Oxidation of **130a** and **130b** with hydrogen peroxide yielded the (methylsulfonyl)-3*H*-furo-pyrimido[1,6-*a*]quinazolin-3-ones **131a**, and **131b.** Alternatively, treatment of **130a** and **130b** with cyclic amines such as piperazine or morpholine afforded the respective amine-linked furo-pyrimido-quinazolinones **132a–**



Scheme 32 Oxidation and amination of furopyrimidoquinazolinones.

d through nucleophilic substitution reactions in which SCH_3 acted as a good leaving group[97] (Scheme 32).

The reactivity of 3*H*-furopyrimidoquinazolinones **123a** and **123b** was investigated by Abu-Hashem[97] through reactions with α-halo-acids. Thus, heating of compounds **123a** and **123b** with 2-chloroacetic acid in $AcOH/Ac_2O$ catalyzed by sodium acetate yielded furo-thiazolo-pyrimido[1,6-*a*]quinazoline-3,5-diones **134a** and **134b**, respectively; these were obtained from the same reactions through the formation of compounds **133a** and **133b** and subsequent condensation. The formation of compounds **134a,b** is not discussed because the mechanism of reduction of the C=N bond of the pyrimidinone ring to complete the cyclization step is unclear. Additionally, condensation of compounds **134a** and **134b** with aryl aldehydes in 1,4-dioxane containing piperidine yielded a series of arylidenes **135a–f**. One-pot reactions of compounds **123a** and **123b** with 2-chloroacetic acid and aryl aldehydes in $AcOH/Ac_2O$ catalyzed by sodium acetate directly afforded the products **135a–f** (Scheme 33).

The alksylation process of 3*H*-furopyrimidoquinazolinones **123a** and **123b** was achieved by treatment of alcoholic potassium hydroxide solutions of the reactants with 3-chloropentane-2,4-dione to afford the desired thiopentane-2,4-diones **136a** and **136b**, respectively. The alkylation of the thione groups of **123a** and **123b** was accomplished after the tautomerization of the thione groups to the thiol forms. Compounds **136a** and **136b** were reacted with hydrazine hydrate, urea and thiourea in 1,4-dioxane containing piperidine at reflux temperature to yield the binary heterocycles **137a**, **137b**, and **138a–d**, respectively. The reactions are cyclocondensations of 1,3-diketones with 1,2- or 1,3-binucleophiles[97] (Scheme 34).

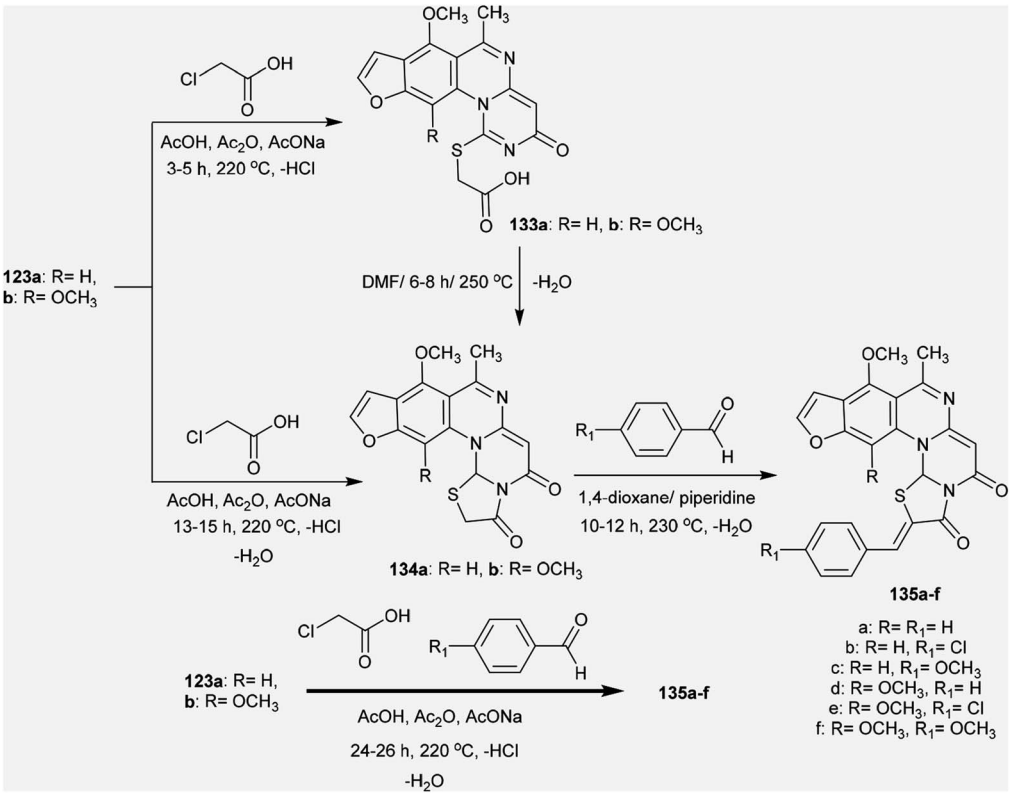
3.2. Reactivity of the amide group

More recently, the tricyclic systems **103c** and **103d** were also prepared under microwave irradiation conditions to improve the yield and shorten the reaction time. The reaction of **102d** to prepare **103d** failed to give a good yield due to the low solubility of the reactant. By dissolving compound **102d** in THF and applying microwave irradiation conditions (20 min at 100 W) with the addition of HMDS with careful stirring, compound **103d** was obtained in 75% yield. On the other side, pyrimidopurine-dione **103c** was synthesized under microwave irradiation conditions from the reaction of pyrimido[1,6-*a*] pyrimidine **102c** with HMDS in 98% yield under the previously described conditions (100 W, 140 °C, 20 min) (Scheme 35).[99]

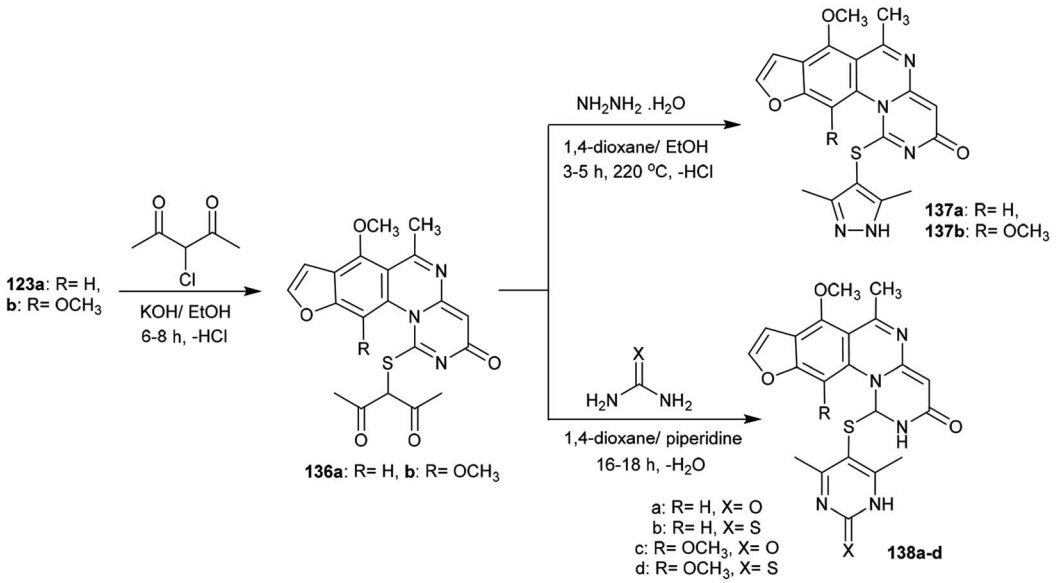
3.3. Nucleophilic substitution reactions

Substitution of the chlorine atom at C3 of tetrahydropyrimidopyrimidines **129a–d** with nucleophiles such as piperazine and morpholine was achieved in boiling methanol to afford the respective 1-aryl-2,4-dimethyl-3,6,8-tri(piperidinyl) and (morpholinyl)-pyrimidopyrimidines **139a–d** (Scheme 36).[98]

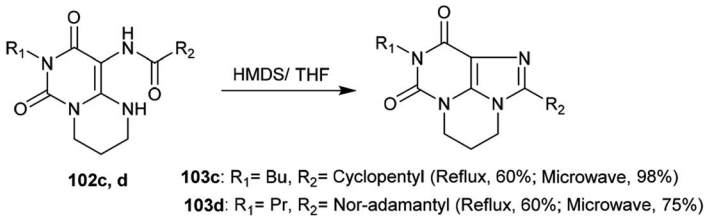
The reactivity of ethyl carboxylate **12a** was verified by reactions with different electrophiles and nucleophiles. Consequently, ethyl carboxylate **12a** was reacted with morpholine,



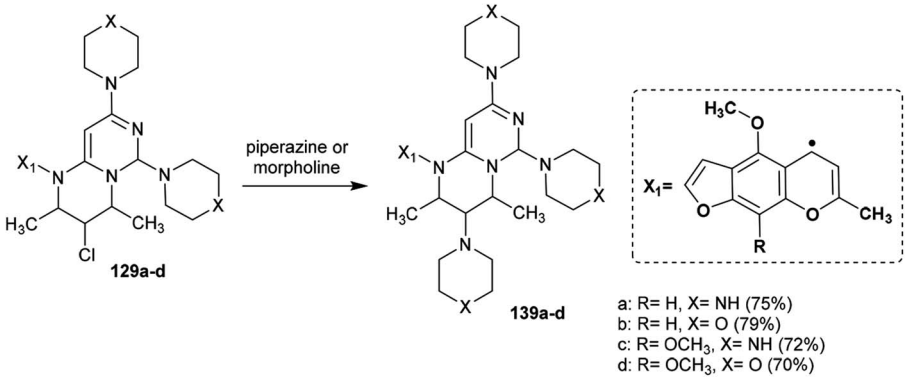
Scheme 33 Synthesis of arylidene of furothiazolo-pyrimido[1,6-*a*]quinazoline-3,5-diones.



Scheme 34 Synthesis of hetrylthio-3*H*-furopyrimidoquinazolinones.



Scheme 35 Synthesis of pyrimidopurine-diones.

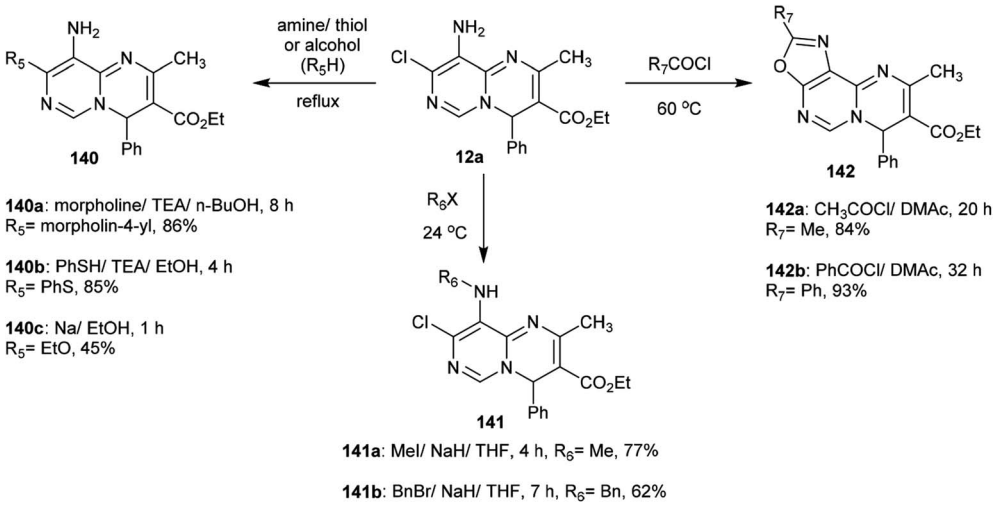


Scheme 36 Synthesis of 1-aryl-3,6,8-trisubstituted-2*H*-pyrimidopyrimidines.

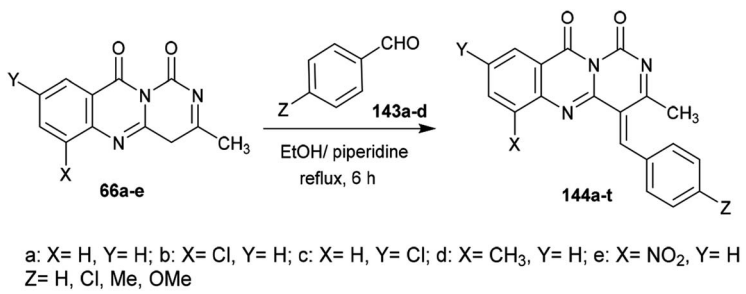
benzenethiol, and sodium ethoxide solutions to afford the anticipated ethyl carboxylates **140a**, **140b**, and **140c**, respectively. In another route, the chlorine atom at C8 of compound **12a** was substituted by reactions with methyl iodide and benzyl bromide to afford the products **141a** and **141b** in 77% and 62% yield, respectively. Additionally, reactions of **12a** with acetyl chloride and benzoyl chloride led to the generation of tricyclic systems, oxazolopyrimidopyrimidines **142a** and **142b**, in 84% and 93% yield, respectively (Scheme 37). The chlorine atom and amino group linked to the basic skeleton of 4*H*-pyrimidopyrimidine provide potential for future studies.[40]

3.4. Condensation reactions

Condensation of 1*H*-pyrimido[6,1-*b*]quinazoline-1,10(4*H*)-diones **66a–e** with aryl aldehydes **143a–d** in ethanol containing piperidine at reflux temperature yielded the respective arylidenes of 3-methyl-1*H*-pyrimido[6,1-*b*]quinazoline-1,10(4*H*)-diones **144a–t** (Scheme 38).[65]



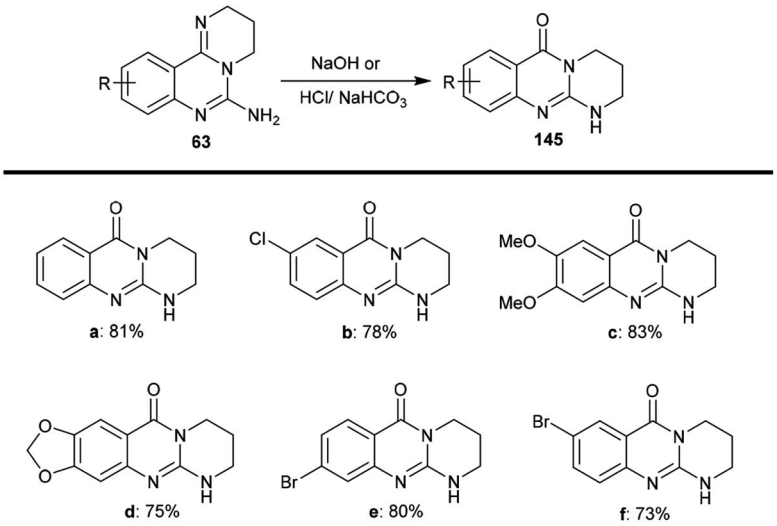
Scheme 37 Reactivity of ethyl 4*H*-pyrimidopyrimidine-carboxylate.



Scheme 38 Synthesis of arylidenes of 3-methyl-1*H*-pyrimido[6,1-*b*]quinazoline-1,10(4*H*)-diones.

3.5. Ring transformations

The selective acidic or basic hydrolysis of substituted-6-amino-3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolines (**63**) furnished the analogue 1,2,3,4-tetrahydro-6*H*-pyrimido[2,1-*b*]quinazolin-6-ones (**145**). The processes involved ring-opening/ring-closing, in which the cleavage of the pyrimidine ring was accomplished in the presence of sodium hydrate and subsequent refluxing in a mixture of ethanol/water to achieve the



Scheme 39 Synthesis of pyrimidoquinazolinones.

intramolecular cyclization. Compounds **145** were obtained with excellent yields ranging from 73% to 83% (Scheme 39).[64]

The sequence of the tentative mechanistic routes of ring-opening/closure for the transformation of pyrimidoquinazolines **63** with the formation of by-products was reported. Therefore, the hydrolysis of **63** in acid medium resulted in cleavage of the pyrimidine ring with the formation of quinazolinones **146**, along with the unexpected formation of pyrimidoquinazolinones **147** as side products. In fact, the intermediates which were formed after the ring-opening process were produced in the hydrochloride form, which hindered the cyclization in the next step. Neutralization of the formed hydrochloride of the anticipated aminoquinazolinone in a refluxing mixture of EtOH/H_2O yielded the tricyclic pyrimido-quinazolinones **145** through simple intramolecular cyclization. Moreover, acetylation of **146** with acetic anhydride in the presence of triethylamine yielded the monoacetylated products **148** in good yields. The basic hydrolysis of the 2*H*-pyrimidine series provides an exceptional and selective route which is superior to acid hydrolysis (Scheme 40).[64]

3.6. Coordination chemistry

The respective pyrimido[1,6-*a*]pyrimidine-dione (**41**) was applied as a tridentate ligand with two oxygen atoms and one nitrogen atom, which can donate electrons to the empty d-orbital of the metal to form three coordination bonds. Therefore, compound **41** tends to form 1 : 1 or 1 : 2 (metal : ligand) metal complexes **149–152** (Scheme 41)[48] by reaction with metal ions such as copper chloride, ferric chloride, cobalt chloride, and lanthanum chloride in methanol at reflux temperature. The metal complexes **149–152** were synthesized by applying the method reported by Merchán *et al.*[100]

4. Biological Activities

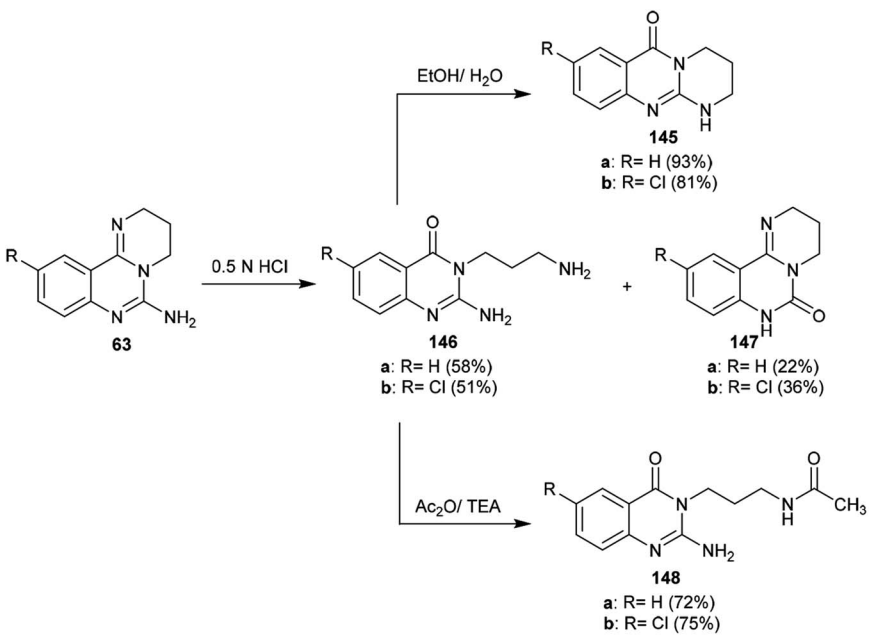
4.1. Cytotoxic Activity

Compounds **54a** and **54f** (Scheme 12) were assessed as anticancer agents against ZR-75-30, HCT116, and A549 cancer cells using the MTT assay. The results revealed that both compounds displayed potent activities against the inspected cell lines. Generally, compound **54f** revealed potent activity against ZR-75-30 cancer cells, with $IC_{50} = 0.71$ μM, HCT116 cancer cells, with $IC_{50} = 1.1$ μM, and A549 cancer cells, with $IC_{50} = 2.2$ μM. Pyrimido[1,6-*c*]quinazoline **54f** was used as a guide compound for further drug development for cancer treatment. The structure–activity relationships revealed that incorporation of the pyrimido[1,6-*c*]quinazoline scaffold is essential for potent cytotoxic results; additionally, the incorporation of a *tert*-butyl substituent at C4′ of the phenyl ring at C6 of the pyrimido[1,6-*c*]quinazoline core enhanced the activity (Fig. 2).[62]

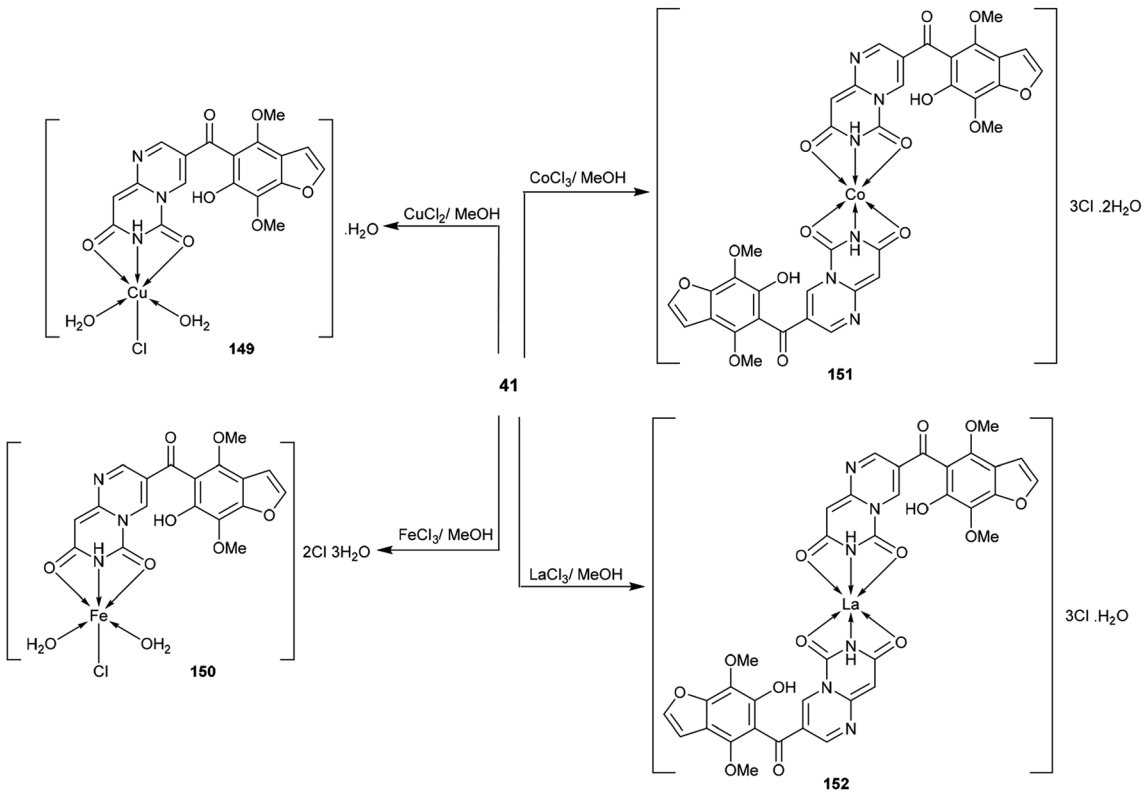
Moreover, the cytotoxic activity was evaluated for pyrimido[1,6-*a*]pyrimidine-dione (**41**) and its metal complexes **149–152** (Schemes 10 and 41) against the hepatocyte cell line by the MTT-based cell viability assay. The results indicated that Cu-complex **149** displayed potent cytotoxicity, with $CC_{50} = 93$ μM relative to VX-950 ($CC_{50} = 90$ μM) against the tested cell line. In general, the formation of complexes is essential for potent cytotoxic results; Fe-complex **150**, Co-complex **151**, and La-complex **152** showed activities of $CC_{50} = 330$, 154, and 213 μM, respectively. Compound **5** showed the lowest cytotoxic activity, with $CC_{50} = 341$ μM. The Cu-, Fe-, Co-, and La- complexes **149–152** could reduce cell viability by 50%.[48]

4.2. Antimicrobial activity

The antimicrobial activity of 6-substituted-2,3-dihydro-4*H*-pyrimido[1,2-*c*]quinazolin-4-ones (**70a–d**) (Scheme 17) was



Scheme 40 Study of the ring-cleavage sequence.



Scheme 41 Synthesis of pyrimido[1,6-*a*]pyrimidine-transition metal complexes.

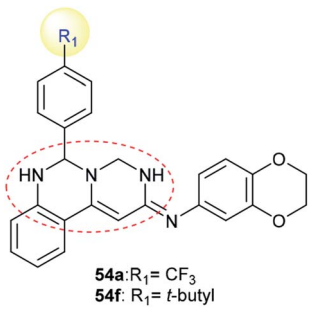


Fig. 2 Structure of potent cytotoxic agents and tyrosine kinase inhibitors.

investigated against *B. cereus*, *B. subtilis*, and *E. coli* as examples of Gram +ve and −ve bacterial strains with *A. niger* as a fungal strain and methaqualone as an antibiotic standard using the disc diffusion technique. Compounds **70a** (MIC = 0.75 × 10^{-3} mmol mL^{-1}) and **70b** (MIC = 0.36 × 10^{-3} mmol mL^{-1}) revealed moderate activities relative to the antibiotic results; however, compounds **70c** (MIC = 0.79 × 10^{-3} mmol mL^{-1}) and **70d** (MIC value = 0.14 × 10^{-2} mmol mL^{-1}) showed weak activity against *B. cereus*. Compound **70b** showed good activity against *B. subtilis* and *E. coli*. Meanwhile, compounds **70b** and **70c** displayed reasonable activities against *Aspergillus niger*.[66]

The antimicrobial activity of quinazolinoquinazolinone **74b** (Scheme 18) was inspected against *S. aureus*, *B. subtilis*, *P. aeruginosa*, *E. coli*, *A. fumigatus*, *G. candidum*, *C. albicans*, and *S. racemosum*. The compound revealed potent results against *S. aureus* and *B. subtilis*, with inhibition zones of 18.2 and 17.3 mm relative to the results of the standard drugs Penicillin G and Streptomycin. In addition, compound **74b** showed moderate activities against the *E. coli* bacterial strain and fungal strains, *i.e*. *A. fumigatus*, *G. candidum*, and *C. albicans*; meanwhile, this compound was found to be inactive against *P. aeruginosa* and *S. racemosum*. The MIC (μg mL^{-1}) was investigated for compound **74b** against different bacterial and fungal strains, in which the MIC was found to be 78 μg mL^{-1} against the *S. aureus* bacterial microorganism and *G. candidum* fungal strain.[68]

The MICs of the anticipated cycloalkyl-pyrimidopyrimidinones **92a–d** and pyrimido[1,6-*a*]pyrimidinone **28** (Schemes 7 and 23) were evaluated against *S. aureus* and *B. subtilis* as Gram-positive bacterial strains, *E. coli* and *P. aeruginosa* as Gram-negative bacterial strains, and *C. albicans* as a fungus. The compounds were prepared with serial dilution at concentrations of 25, 50, 100, 200, and 400 μg mL^{-1}. Ciprofloxacin and Triflucan were used as antibiotic standards. The compounds showed moderate MIC activities against the tested microbial strains. The MIC inhibits the growth of visible colonies, by which *S. aureus* was found to be the most resistant microorganism. The MIC was found to be ≥ 1600 μg mL^{-1} against *S. aureus* for all the inspected compounds and ≥ 800 μg mL^{-1} against the other microorganisms.[75]

The antibacterial activities of compounds **123a,b**, **130a,b**, **131a,b**, **132a–d**, **133a,b**, **134a,b**, **135a–f**, **136a,b**, **137a,b**, and **138a–d** (Schemes 29 and 32–34) were evaluated against *S.*

aureus, *S. pyogenes*, *E. coli*, and *K. pneumoniae* using cefotaxime sodium as antibiotic standard. Compounds **135a–f**, **137a,b**, and **138a–d** revealed potent activities against the inspected bacterial strains. The remaining compounds displayed moderate activities. On the other hand, two series of compounds, **135a–f** and **138a–d**, have potent antifungal activities against *A. Niger*, *A. Alternata*, *C. Lunata*, and *C. Albicans* fungal strains, with MICs of 2–9 μmol mL^{-1} and 7–12 μmol mL^{-1}, respectively. The SAR studies verified that potent antimicrobial results were achieved by the incorporation of alkyl groups such as methyl, electron-donating groups such as thioxo, hydroxyl, methoxy, amino, methylsulfonyl, and chlorine atom, heterocyclic cores such as thiazole, pyrazole, pyrimidine, and quinazoline, and cyclic amines such as piperazine and morpholine rings.[97]

The antibacterial activity of the desired arylidenes of 3-methyl-1*H*-pyrimido[6,1-*b*]quinazoline-1,10(4*H*)-diones **144a–t** was evaluated using the agar cup technique against *E. coli* and *S. typhi* Gram-negative strains. The results showed that the compounds have more potent activity against *E. coli* than against the strain of *S. typhi*. In addition, compounds **144e** (X = H, Y = NO_2, Z = H), **g** (X = Cl, Y = H, Z = Cl), **h** (X = H, Y = Cl, Z = Cl), **j** (X = H, Y = NO_2, Z = Cl), **o** (X = H, Y = NO_2, Z = CH_3), and **t** (X = H, Y = NO_2, Z = OCH_3) demonstrated potent activity relative to the standard antibiotic penicillin (24 mm). The antifungal activity was investigated by poison plate assays[101] against *A. niger* and *P. chrysogenum* fungal strains. No growth of the fungal strains was noted for compounds **144b**, **c**, **e**, **g**, **h**, **j**, **l**, **m**, **o**, **q**, **r**, or **t** (Scheme 38).[65]

4.3. Antihyperglycemic and antihyperlipidemic potentials

Antihyperglycemic and antihyperlipidemic tests were carried out for compound **92b** using albino mice and pregnant female albino rats. The test was performed using six groups of eight male albino mice; one group served as a control, and the other groups were administered the inspected compound by gastric tube in regularly increasing doses (200, 400, 600, 800 and 1000 mg per kg b.w.). Accordingly, pyrimidoquinazolinone **92b** (Scheme 23) was investigated as an anti-hyperglycemic, anti-hyperlipidemic and antioxidant agent using a sublethal dose of 10 mg per kg b.w. per day for three weeks; it was found to be a potent agent, showing good results in neonatal streptozotocin-induced (n-STZ) diabetic male and female albino rats. The potent results can be attributed to the insulinogenic action and extrapancreatic effects in addition to the improving action on the antioxidant defense system.[75]

4.4. Antidiabetic and antioxidant activities

The antidiabetic and antioxidant effects were assessed for pyrimidoquinazolinone **92b** (Scheme 23); the results indicated that the compound displayed potent antihyperglycemic and anti-hyperlipidemic potentials in n5-STZ-induced type 2 diabetic male and female rats. The effects are related to the insulinogenic action and extrapancreatic properties in addition to the improving action on the antioxidant defense system. However, additional clinical research is necessary to estimate the safety and effectiveness of the investigated compound in diabetic human beings.[102]

4.5. Gastroprotective agents

In this type, pyrazolopyrimidopyrimidines **99a**, **99b**, **99f**, and **99g** (Scheme 24) were evaluated as gastroprotective agents against gastric ulcer induced by HCl/ethanol solution. The samples were tested at two different concentrations (50 and 100 mg kg^{-1}). The results demonstrated that the tricyclic pyrazolo-pyrimido-pyrimidine **99f** at a concentration of 100 mg kg^{-1} showed remarkably higher inhibition of gastric lesions (91.42%) relative to the results obtained by cimetidine (74.03% at 100 mg kg^{-1}), which was utilized as a reference drug. The structure–activity relationships (SARs) specified that the replacement of hydrogen atom with methyl substituents is necessary for potent gastroprotective results in addition to the presence of the pyrazolopyrimidopyrimidine skeleton, which improves the biological results.[79]

4.6. Anticonvulsant activity

The advanced detection and progress of new chemical agents for the remediation of epilepsy is based on the use of predictable animal models, whereby MES and scPTZ-induced seizure models in mice are known as reference standards in the primary periods of testing. Two series of thienopyrimidoquinazolinones **115a–o** and pyridopyrimidoquinazolinones **119a–u** (Schemes 27 and 28 and Fig. 3)[92,96] were assessed as anticonvulsant agents (anti-MES and anti-scPTZ). The compounds showed potent activities. The neurotoxicity was evaluated through a Rotarod procedure. All tested intraperitoneal compounds were administered in different doses ranging from 15 to 175 mg per kg b.w., medium toxic dose values (DT50) and post-summer protection. The substituents attached to the heterocyclic and aromatic benzene rings have high impacts on the biological characteristics, in which the groups responsible for the penetration across the blood–brain barrier arise from modulating the lipophilicity. The protection index (PI) values indicate the relationship between lipophilicity and toxicity. Compounds **119j** and **119n** revealed potent activities. More potent activity against seizures induced by scPTZ than against seizures induced by MES was noted for compounds **115a–o**. Additionally, compounds **119a–u** revealed greater decreases in activity against seizure induced by scPTZ than against seizure induced by MES. The structures and SARs of the anticonvulsant activity of the thieno- and pyrido-fused pyrimidoquinazolinones **115a–o** and **119a–u** are specified in Fig. 3.[103,104]

4.7. Anti-inflammatory activity

The respective pyrazolopyrimidopyrimidines **99a**, **99b**, **99f**, and **99g** (Scheme 24) were evaluated as anti-inflammatory agents using carrageenan-induced rat paw edema assessments. The results presented that the most potent analogs are compounds **99a**, **99b**, and **99f** (50-100 mg kg^{-1}, i.p.) relative to the results of the reference drug, acetylsalicylic-lysine (300 mg kg^{-1}, i.p.). The most potent anti-inflammatory analog is **99f**. The percent inhibition for compound **99f** ranged from 60.02% to 82.83%

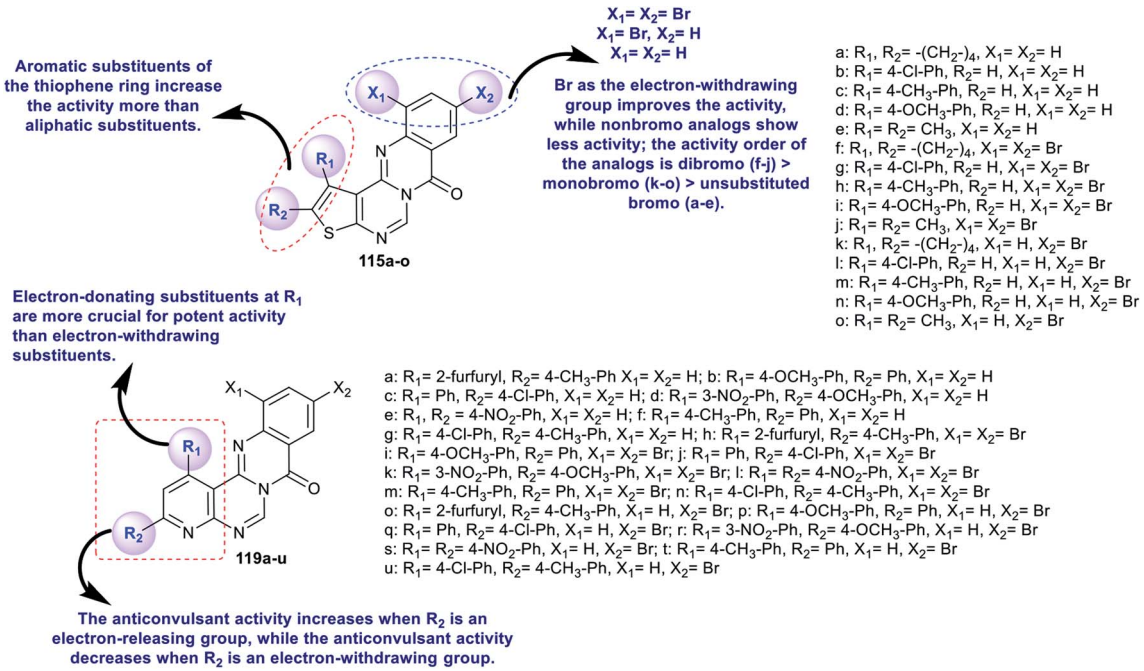


Fig. 3 Structures and SARs of the potent anticonvulsant agents.

three hours after injection of the carrageenan and reduction of edema. The nature of the substituents of pyrazolopyrimidopyrimidines affected the obtained results of the anti-inflammatory activities of the inspected compounds. Consequently, replacement of the hydrogen atom at position 5 with methyl or ethyl groups and replacement of the nitrile group with an ester function is essential for potent anti-inflammatory activity.[79]

The anti-inflammatory activities of pyrimidopyrimidines **129** and **139a–d** (Scheme 36 and Fig. 4) were evaluated by a carrageenan-induced paw edema assay using diclofenac sodium as a standard drug. The results obviously indicated that most of the compounds have potent activities relative to those obtained by diclofenac sodium after 1–3 hours. Compounds **129** and **139a–d** inhibited carrageenan-induced paw edema at 59.4–62.3% (after 1 hour), 59.1–61.6% (after 2 hours), and 42.2–48.5% (after 3 hours). As a result, pyrimido[1,6-*a*]pyrimidines **139a–d** are generally more potent than compounds **129a–d**. The substitution of a chlorine atom at C3 of pyrimido[1,6-*a*]pyrimidines **129a–d** with cyclic amines is crucial for potent anti-inflammatory activity. In addition, the order of the activities of compounds **139a–d** was noted to be **139c** > **139a** > **139d** > **139b**. Therefore, the presence of methoxy substituents (compound **139c**) instead of unsubstituted analogs is necessary for potent anti-inflammatory activity. Moreover, piperazine

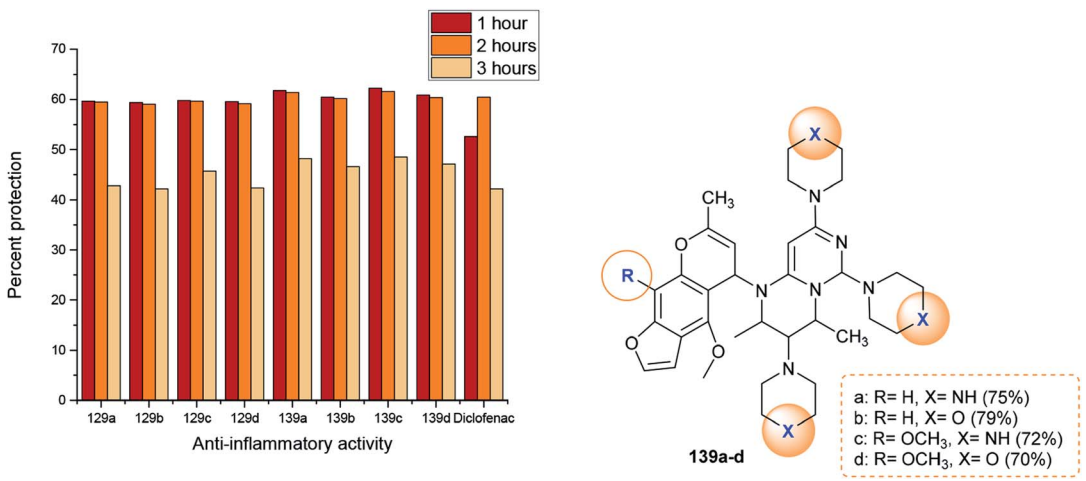


Fig. 4 Comparison of the anti-inflammatory activities of 2*H*-pyrimido[1,6-*a*]pyrimidines.

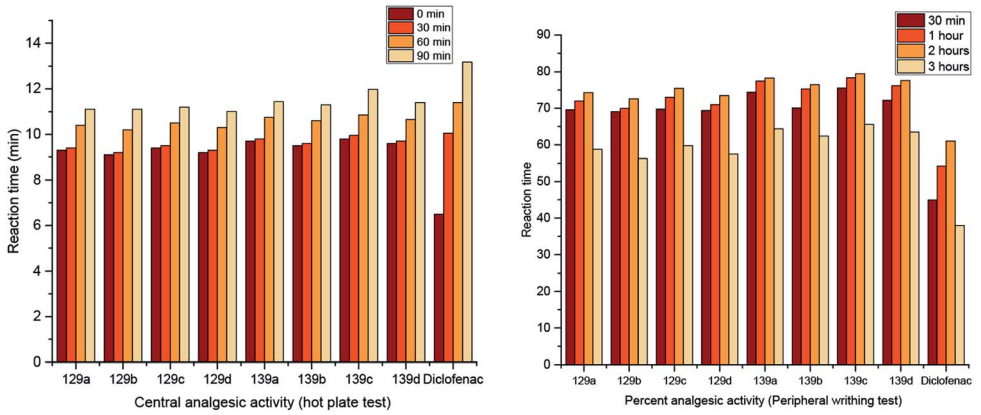


Fig. 5 Comparison of the analgesic activity results using hot plate and peripheral writhing tests.

substituents are better than morpholine substituents for potent activity.[98]

4.8. Analgesic activity

Two series of pyrimidopyrimidines, **129** and **139a–d** (Scheme 36 and Fig. 5), were evaluated as analgesic agents by the hot-plate (central analgesic activity) and acetic acid-induced writhing tests. The compounds showed potent activities using both methods compared to the results obtained for diclofenac sodium. Hence, pyrimidopyrimidine **139c** displayed higher analgesic activity than diclofenac sodium. The SARs indicated that the incorporation of methoxy substituents at C9 of the furochromenyl core is essential for potent activity. The efficiency of the tested analgesic agents increases with time and subsequently decreases after three hours. Frequently, pyrimidopyrimidines **139a–d** are more potent agents than pyrimidopyrimidines **129a–d**. These results can be explained by the action of the chemical structures. Accordingly, the substitution of the chlorine atom at C3 with the piperazine ring of the pyrimidopyrimidine core is essential for potent results of analgesic activity.[98]

4.9. Antiviral activity

The pyrimidopyrimidine-dione **41** and its metal complexes **149–152** (Schemes 10 and 41) were evaluated as HIV agents using Atevirdine as an antibiotic standard. The compounds displayed good activities relative to the antibiotic standard. Compound **41** presented the most potent activity, with IC_{50} = 40.31 μM; meanwhile the metal complexes **149–152** revealed IC_{50} values ranging from 78.67 to 96.18 μM. The tested compounds generally indicated respectable HIV-1 RT inhibitory activity but showed lower activities compared to Atevirdine. On the other hand, compound **41** and its metal complexes **149–152** presented potent HCV NS3-4A protease inhibitory activities, with IC_{50} = 0.388, 0.445, 0.987, 0.456, and 0.765 μM, respectively, relative to the results of the standard VX-950 (IC_{50} = 0.20 μM). The complexation step generally improves the activity against HCV NS3-4A protease; however, in this case, the complexation step of compound **41** decreases the activities of the formed metal complexes to a lower degree.[48]

4.10. Kinase inhibitory activity

Pyrimido[1,6-*c*]quinazoline **54f** (Scheme 12) was evaluated as an inhibitor for protein tyrosine kinases such as FLT3, INSR, and VEGFR-2, with potent results. The IC_{50} values ranged from 0.94 to 0.86 and 1.0 μM against FLT3, INSR and VEGFR-2 protein tyrosine kinases, respectively. In addition, pyrimido[1,6-*c*]quinazoline **54a** showed no activity against any of the tested kinases.[62] Also, INSR and VEGFR-2 are closely related to breast cancer.[105,106]

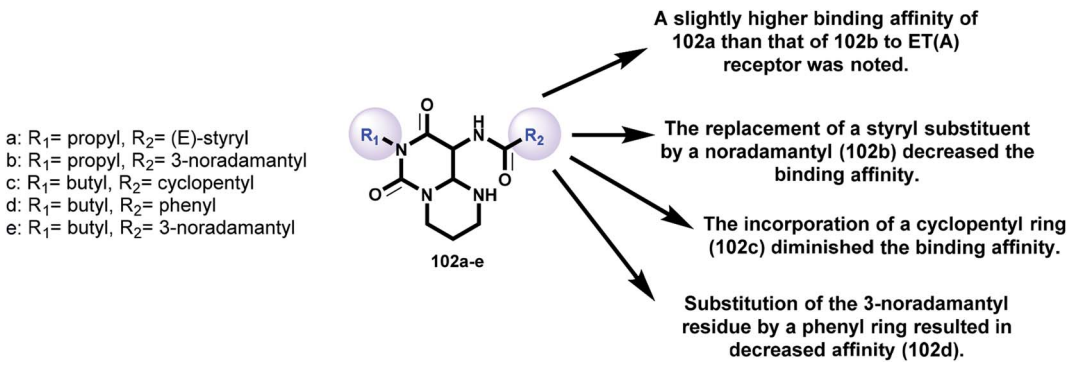


Fig. 6 SARs of pyrimidopyrimidine-diones as bioactive molecules.

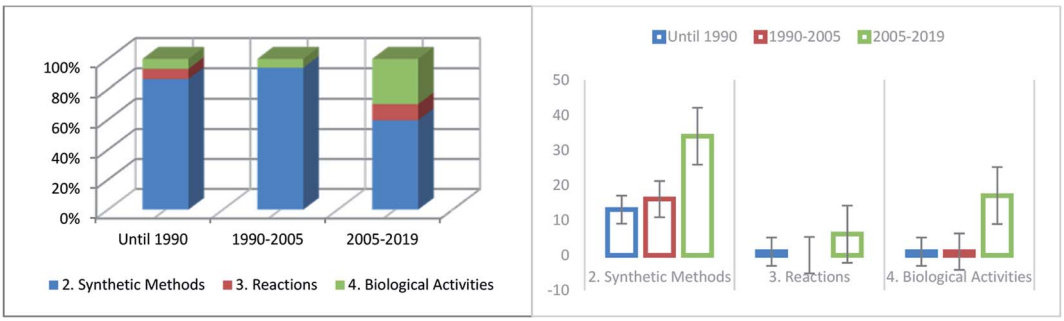


Fig. 7 Comparison of the number of reports related to the different sections of this paper in the last decade.

4.11. Affinity for ET(A) receptors

Griessmeier and Müller[107] demonstrated the affinities of a series of substituted 6*H*-pyrimidopyrimidine-diones **102** (Scheme 25 and Fig. 6) as receptors for endothelin ET(A)-selective antagonists against human astrocytoma 1321N1 cell lines by applying [^{3}H]BQ-123. The affinity was found to be moderate, with [^{3}H]BQ-123 binding inhibition in the range of 30–40% at a definite concentration. The radioligand binding inhibition was determined to be 10 μmol l^{-1} [^{3}H]BQ-123. The inhibition of radioligand binding indicated that compound **102a** displayed moderate affinity to ET(A) receptors in human astrocytoma 1321N1 cells, with values of 33% for **102a**, 20% for **102b**, 2% for **102c**, 14% for **102d**, and 35% for **102e** (Fig. 6) against the human astrocytoma 1321N1 cell line. The expression level of ET(A) receptors for the prepared membranes of the cell line was found to be high (B_{max} = 128 fmol mg^{-1} protein). The K(D) value for [^{3}H]BQ-123 (K_D = 2.29 nmol l^{-1}) was equivalent to that previously investigated in the human neuroblastoma SK-N-MC cell line. The rank order of a series of agonists and antagonists clarified the individual labeling of ET(A) receptors on the studied cell line "astrocytoma 1321N1" by [^{3}H]BQ-123. Astrocytoma 1321N1 cells are useful for screening potential ET(A) ligands in radioligand binding assessments with [^{3}H]BQ-123; these cells express high levels of ET(A) receptors.

5. Concluding remarks

The present survey provides a description of the chemistry and biological importance of heterocycles incorporating pyrimido[1,6-*a*]pyrimidine and pyrimido[1,6-*c*]pyrimidine scaffolds. The pyrimido-pyrimidines of this class demonstrated valuable and diverse biological properties. The investigated compounds were synthesized through the formation of three C–N bonds by the reaction of acyclic reactants such as 1,3-diamine with 4-isothiocyanato-4-methylpentan-2-one. In another route, one-pot multicomponent reactions of aminopyrimidines, aldehydes, and β-ketoesters yielded the substituted analogs. Pyrimidopyrimidines were also synthesized from the reaction of aminopyrimidines with unsaturated esters, unsaturated ketones or Meldrum's acid. In addition, pyrimidine-2,4(1*H*,3*H*)-diones were synthesized from uracil, and 4,6-dichloropyrimidine served as a reactive synthon for the synthesis of pyrimido[1,6-*c*] quinazolines. Also, the chlorination of 6-bromo-2-substituted-quinazolinones and subsequent reaction with 2-amino-5-bromobenzoic acid yielded the respective quinazolino-quinazolinones. Cyclization of the respective 4-(3-hydroxy-propyl-amino)-quinazolines in hydrochloric acid produced the quaternary salts. In another route, pyrimidopurine-diones were prepared from 5,6-diamino-3-substituted-pyrimidine-diones by amidation or condensation with acids and cyclization with 1,3-dibromopropane. Moreover, tri-, tetracyclic, and binary heterocycles were synthesized. These studies reported the reactivity of the substituents, nucleophilic substitution reactions, condensations, ring transformations, and complex formation. The different synthetic methods investigated for the construction of the pyrimidopyrimidine ring provide various heterocycles that are useful in different areas of chemistry, such as drug design. Consequently, the compounds are potent cytotoxic, antimicrobial, antihyperglycemic, antihyperlipidemic, antidiabetic, antioxidant, gastroprotective, anticonvulsant, anti-inflammatory, analgesic, and antiviral agents and act as inhibitors of protein tyrosine kinases. Preferred structures can bind to several high-affinity targets, affording novel biologically active agents. Thus, pyrimido[1,6-*a*]pyrimidines and pyrimido[1,6-*c*]pyrimidines represent substantial characteristic scaffolds that possess a wide range of biological characteristics.

6. Literature overview

Since Yani and coworkers[24] reported the synthesis of 2,3,4,7-tetrahydro-6*H*-pyrimido[1,6-*a*]pyrimidin-6-ones, several scientific studies have been published regarding the synthesis of this category of heterocyclic compounds. Several surveys have demonstrated the frequency with which published work relating to the diverse sections of this paper has increased throughout the preceding period (Fig. 7). During this period (before 1990), much interest was aroused in the preparation of compounds with the same biological behavior as pyrimidopyrimidine isomers [4,5-*d*] and [5,4-*d*]. The numbers of synthetic methods (Section 2) and reactions (Section 3) have remarkably increased in recent years owing to the significant and valuable biological activities of these compounds. The biological applications (Section 4) have increased in recent years, although several types of biological characteristics have not been yet applied.

7. Future perspectives

The diverse biological activities which have been attributed to pyrimidopyrimidines and pyridopyrimidine analogs should be applied to this class of compounds depending on the nature of the substituents attached to the basic ring skeleton. Therefore, the pyrimido[1,6-*a*]pyrimidine-6,8(7*H*)-dione moiety provides a possible ligand for the formation of complexes, which are potent cytotoxic agents; further evaluation of their cytotoxic and antiviral activities should be a research focus. Compounds incorporating the pyrimido[1,2-*c*]quinazolinone scaffold are potent antimicrobial agents; this provides further areas of study for the synthesis of a series of these compounds with the same potency. The cycloalkyl[*e*]pyrimidopyrimidinone compounds have potent antihyperglycemic, antihyperlipidemic, antidiabetic, and antioxidant activities; the tricyclic system of pyrimidopyrimidine fused with a cycloalkane ring provides efficient bioactive components. Furthermore, tricyclic pyrazolo-pyrimido[1,2-*c*]pyrimidin-4(8*H*)-imines display potent gastroprotective activities. In addition, thieno-pyrimidoquinazolinones **115a–o** and pyrido-pyrimidoquinazolinones **119a–u** are potent anticonvulsant agents; this provides a route to prepare biologically active compounds with diverse activities and to achieve potent results. The attachment of cyclic amines and binary heterocycles to pyrimido[1,6-*a*]pyrimidine skeletons is an efficient synthetic route to prepare compounds with anti-inflammatory and analgesic activities. The compounds of pyrimidopyrimidines and pyridopyrimidines are potent inhibitors of protein kinase; therefore, 2-imino-pyrimidoquinazolines are potent inhibitors of protein tyrosine kinases.

Abbreviations

EeAChE	Electrophorus electricus acetylcholinesterase
hAChE	Human acetyl-cholinesterase
hBChE	Human butyryl-cholinesterase
CF_3SO_3H	Trifluoromethanesulfonic acid
equiv.	Equivalent
DOWTHERM™A	A eutectic mixture of two very stable compounds
$Pd(OH)_2$	Palladium hydroxide
K_2CO_3	Potassium carbonate
DMF	*N*,*N*-Dimethylformamide
$POCl_3$	Phosphorus oxychloride
TEA	Triethylamine
Boc_2O	Boc anhydride or di-*tert*-butyl pyrocarbonate
$NaBH_4$	Sodium borohydride
$SOCl_2$	Thionyl chloride
$HC(OEt)_3$	Triethyl orthoformate
HCOOH	Formic acid
PPA	Polyphosphoric acid
MW	Microwave
Zn	Zinc
NaH	Sodium hydride
THF	Tetrahydrofuran
MeI	Methyl iodide
ZR-75-30	Human breast cancer cells
HCT116	Human cancer colon cells
A549	Human lung cancer cells
IC_{50}	Inhibitive concentration at 50% of the original concentration
MIC	Minimum inhibitory concentration
EDC	*N*′-(3-Dimethyl-aminopropyl)-*N*-ethylcarbodiimide-hydrochloride
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
MES	Maximum electroshock-induced seizures
scPTZ	Subcutaneous pentylenetetrazole
PI	Protection index

Gram-positive bacteria

S. aureus	*Staphylococcus aureus*
B. subtilis	*Bacillus subtilis*
B. cereus	*Bacillus cereus*
S. pyogenes	*Streptococcus pyogenes*

Gram-negative bacteria

P. aeruginosa	*Pseudomonas aeruginosa*
E. coli	*Escherichia coli*
K. pneumoniae	*Klebsiella pneumoniae*
S. typhi	*Salmonella typhi*

Fungal strains

A. fumigatus	*Aspergillus fumigatus*
A. niger	*Aspergillus niger*
G. candidum	*Geotrichum candidum*
C. albicans	*Candida albicans*
S. racemosum	*Syncephalastrum racemosum*
A. alternata	*Alternaria alternata*
C. lunata	*Curvularia lunata*
P. chrysogenum	*Penicillium chrysogenum*
CC_{50}	50% cytotoxic concentration

Conflicts of interest

The authors declare no conflict of interest.

References

1 R. Abdel-Rahman and K. El-Mahdy, *Heterocycles*, 2012, **85**(10), 2391–2414, DOI: 10.3987/REV-12-745.
2 F. F. Solca, A. Baum, E. Langkopf, G. Dahmann, K.-H. Heider, F. Himmelsbach and J. C. A. van Meel, *J. Pharmacol. Exp. Ther.*, 2004, **311**, 502–509, DOI: 10.1124/jpet.104.069138.
3 J. P. De la Cruz, T. Carrasco, G. Ortega and F. S. De la Cuesta, *Lipids*, 1992, **27**(3), 192–194.

4 M. G. Gebauer, C. Mc Kinlay and J. E. Gready, *Eur. J. Med. Chem.*, 2003, **38**(7–8), 719–728.
5 Y. Fang, J. Xu, Z. Li, Z. Yang, L. Xiong, Y. Jin, Q. Wang, S. Xie, W. Zhu and S. Chang, *Bioorg. Med. Chem.*, 2018, **26**(14), 4080–4087.
6 M. Simcox, B. Higgins, L. McDermott, T. Nevins, K. Kolinsky, M. Smith, H. Yang, J. Li, Y. Chen and K. Luk, *Eur. J. Cancer Suppl.*, 2004, **2**(8), 59.
7 H. C. Barlow, K. J. Bowman, N. J. Curtin, A. H. Calvert, B. T. Golding, B. Huang, P. J. Loughlin, D. R. Newell, P. G. Smith and R. J. Griffin, *Bioorg. Med. Chem. Lett.*, 2000, **10**(6), 585–589.
8 A. H. Bacelar, M. A. Carvalho and M. F. Proença, *Eur. J. Med. Chem.*, 2010, **45**(7), 3234–3239.
9 P. Raddatz and R. Bergmann, *Ger. Pat.* 360731, 1988Chem. Abstr. 109, 54786.
10 N. Kitamura and A. Onishi, *Eur. Pat.* 163599, 1984Chem. Abstr. 104, 186439.
11 (*a*) P. Sharma, N. Rane and P. Pandey, *Arch. Pharm.*, 2006, **339**(10), 572–578, DOI: 10.1002/ardp.200600067; (*b*) P. Sharma, N. Rane and V. K. Gurram, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4185–4190, DOI: 10.1016/j.bmcl.2004.06.014.
12 (*a*) S. P. Iadonato, K. Bedard, M. W. Imanaka and K. W. Fowler, WO 2013049352 A2 20130404. PCT Int. Appl. 2013; (*b*) A. C. Krueger, D. L. Madigan, D. W. Beno, D. A. Betebenner, R. Carrick, B. E. Green, W. He, D. Liu, C. J. Maring, K. F. McDaniel, H. Mo, A. Molla, C. E. Motter, T. J. Pilot-Matias, M. D. Tufano and D. J. Kempf, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2212–2215, DOI: 10.1016/j.bmcl.2012.01.096.
13 (*a*) Y. Tong, T. D. Penning, A. S. Florjancic, J. Miyashiro and K. W. Woods, *US. Pat.* Appl. 0220572, 2012; (*b*) S. M. El-Moghazy, D. A. Ibrahim, N. M. Abdelgawad, N. A. H. Farag and A. S. El-Khouly, *Sci. Pharm.*, 2011, **79**(3), 429–447; (*c*) T. J. Delia, M. Baumann and A. Bunker, *Heterocycles*, 1993, **35**, 1397–1410.
14 J. R. Doherty, C. Yang, K. Scott, M. D. Cameron, M. Fallahi, W. Li, M. A. Hall, A. L. Amelio, J. K. Mishra, F. Li, M. Tortosa, H. M. Genau, R. J. Rounbehler, L. Yungi, C. V. Dang, K. G. Kumar, A. A. Butler, T. D. Bannister, A. T. Hooper, K. Unsal-Kacmaz, W. R. Roush and J. L. Cleveland, *Cancer Res.*, 2014, **74**(3), 908–920, DOI: 10.1158/0008-5472.
15 H. Wang, C. Yang, J. R. Doherty, W. R. Roush, J. L. Cleveland and T. D. Bannister, *J. Med. Chem.*, 2014, **57**, 7317–7324, DOI: 10.1021/jm500640x.
16 M. W. Martin, J. Newcomb, J. J. Nunes, C. Boucher, L. Chai, L. F. Epstein, T. Faust, S. Flores, P. Gallant, A. Gore, Y. Gu, F. Hsieh, X. Huang, J. L. Kim, S. Middleton, K. Morgenstern, A. Oliveirados-Santos, V. F. Patel, D. Powers, P. Rose, Y. Tudor, S. M. Turci, A. A. Welcher, D. Zack, H. L. Zhao, L. Zhu, X. T. Zhu, C. Ghiron, M. Ermann and D. Johnston, *J. Med. Chem.*, 2008, **51**(6), 1637–1648.
17 V. J. Ram, A. Goel, S. Sarkhel and P. R. Maulik, *Bioorg. Med. Chem.*, 2002, **10**, 1275–1280.
18 G. W. Rewcastle, A. J. Bridges, D. W. Fry, J. R. Rubin and W. A. Denny, *J. Med. Chem.*, 1997, **40**(12), 1820–1826.
19 S. N. Sirakanyan, D. Spinelli, A. Geronikaki, E. K. Hakobyan, H. Sahakyan, E. Arabyan, H. Zakaryan, L. E. Nersesyan, A. S. Aharonyan, I. S. Danielyan, R. E. Muradyan and A. A. Hovakimyan, *Molecules*, 2019, **24**(21), E3952, DOI: 10.3390/molecules24213952.
20 D. S. Rina, M. S. Nirmal and C. R. Vivek, *Asian J. Appl. Chem. Res.*, 2018, **1**(1), 1–9.
21 C. M. G. Tanarro and M. Gutschow, *J. Enzyme Inhib. Med. Chem.*, 2011, **26**(3), 350–358, DOI: 10.3109/14756366.2010.504674.
22 F. Dennin, D. Blondeau and H. Sliwa, *J. Heterocycl. Chem.*, 1990, **27**(7), 1963–1967, DOI: 10.1002/jhet.5570270721.
23 A. Vasudevan, F. Mavandadi, L. Chen and A. Gangjee, *J. Org. Chem.*, 1999, **64**, 634–638, DOI: 10.1021/jo9713870.
24 M. Yani, S. Takeda, T. Baba and K. Kitagawa, *Yakugaku Zasshi*, 1974, **94**(12), 1503–1514, DOI: 10.1248/yakushi1947.94.12_1503.
25 I. Zh. Lulle, R. A. Paégle, I. B. Mazheika and M. Yu. Lidak, *Chem. Heterocycl. Compd.*, 1983, **19**(4), 439–446, DOI: 10.1007/BF00516219.
26 B. Stanovnik, H. V. De Bovenkamp, J. Svete, A. Hvala, I. Simonič and M. Tišler, *J. Heterocycl. Chem.*, 1990, **27**(2), 359–361.
27 I. E. Kuznetsov, D. K. Susarova, L. A. Frolova, A. S. Peregudov, A. F. Shestakov, S. I. Troyanov, K. J. Stevenson and P. A. Troshin, *Chem. Commun.*, 2017, **53**, 4830–4833, DOI: 10.1039/c6cc10179h.
28 C. Chapuis, H. Hagemann, W. Fieber, R. Brauchli and J.-Y. de Saint Laumer, *J. Phys. Org. Chem.*, 2009, **22**, 282–288, DOI: 10.1002/poc.1465.
29 (*a*) L. Vasvári-debreczy, I. Hermecz and P. Mátyus, Bicyclic 6-6 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 1:1, *Compr. Heterocycl. Chem. II*, 1996, **8**, 633–706, DOI: 10.1016/B978-008096518-5.00192-1; (*b*) I. Hermecz and L. Vasvári-Debreczy, Bicyclic 6-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 1:1, *Compr. Heterocycl. Chem. II*, 2008, **12**, 257–320, DOI: 10.1016/B978-008044992-0.01104-4.
30 M. Monier, D. Abdel-Latif, A. El-Mekabaty and K. M. Elattar, *Mini-Rev. Org. Chem.*, 2019, **16**, 1–23, DOI: 10.2174/1389557519666190925161145.
31 M. Monier, D. Abdel-Latif, A. El-Mekabaty and K. M. Elattar, *RSC Adv.*, 2019, **9**, 30835–30867, DOI: 10.1039/C9RA05687D.
32 D. D. Ivy, J. P. Kinsella, J. W. Ziegler and S. H. Abman, *J. Thorac. Cardiovasc. Surg.*, 1998, **115**(4), 875–882.
33 K. M. Elattar and B. D. Mert, *RSC Adv.*, 2016, **6**, 71827–71851, DOI: 10.1039/C6RA12364C.
34 M. Monier, D. Abdel-Latif, A. El-Mekabaty, B. D. Mert and K. M. Elattar, *Curr. Org. Synth.*, 2019, **16**(6), 812–854, DOI: 10.2174/1570179416666190704113647.
35 K. M. Elattar, R. Rabie and M. M. Hammouda, *Synth. Commun.*, 2016, **46**, 1477–1498.
36 K. M. Elattar, R. Rabie and M. M. Hammouda, *Monatsh. Chem.*, 2017, **148**, 601–627, DOI: 10.1007/s00706-016-1852-1.

37 A. A. Fadda, S. A. El-Hadidy and K. M. Elattar, *Synth. Commun.*, 2015, **45**(24), 2765–2801, DOI: 10.1080/00397911.2015.1089577.
38 G. Zigeuner, W.-B. Lintschinger, A. Fuchsgruber and K. Kollmann, *Monatsh. Chem.*, 1976, **107**, 171–181.
39 A. Alizadeh, J. Mokhtari and M. Ahmadi, *Tetrahedron*, 2012, **68**, 319–322.
40 J. Xiang, H. Li, K. Yang, L. Yi, Y. Xu, Q. Dang and X. Bai, *Mol. Diversity*, 2012, **16**, 173–181, DOI: 10.1007/s11030-011-9345-y.
41 A. M. Hussein, *J. Heterocycl. Chem.*, 2012, **49**(2), 446–451.
42 F. Delnnin, D. Bulndeau and H. Sliwa, *Tetrahedron Lett.*, 1989, **30**(12), 1529–1530.
43 H. M. Hassneen and T. A. Abdallah, *Molecules*, 2003, **8**(3), 333–341, DOI: 10.3390/80300333.
44 M. H. Elnagdi, E. A. Abdel-All and G. E. H. Elgemeie, *Heterocycles*, 1985, **23**(12), 3121–3153, DOI: 10.3987/R-1985-12-3121.
45 S. M. Sherief and A. M. Hussein, *Monatsh. Chem.*, 1997, **128**(6–7), 687–696, DOI: 10.1007/BF00807600.
46 K. C. Joshi, Y. N. Pathak and U. Grage, *J. Heterocycl. Chem.*, 1979, **16**(6), 1141–1145, DOI: 10.1002/jhet.5570160611.
47 I. H. El Azab and K. M. Khaled, *Russ. J. Bioorg. Chem.*, 2015, **41**(4), 421–436.
48 S. A. Galal, A. S. Abd El-All, K. H. Hegab, A. A. Magd-El-Din, N. S. Youssef and H. I. El-Diwani, *Eur. J. Med. Chem.*, 2010, **45**, 3035–3046.
49 P. Kaure, R. Kaur and K. Kaur, *J. Global Pharma Technol.*, 2009, **2**(4), 35–39.
50 (*a*) M. A. Al-Omar, A. S. El-Azab, S. G. Abdel Hamide and H. A. El-Obeid, *J. Saudi Chem. Soc.*, 2005, **10**, 113–128; (*b*) M. A. Al-Fayez, A. M. Aleisa and M. A. Al-Omar, *J. Biol. Sci.*, 2007, **7**, 532–538, DOI: 10.3923/jbs.2007.532.538.
51 F. M. Refaie, A. Y. Esmat, S. M. A. Gawad, A. M. Ibrahim and M. A. Mohamed, *Lipids Health Dis.*, 2005, **4**, 22, DOI: 10.1186/1476-511X-4-22.
52 D. Murugesan, S. Periyaswamy, D. Erik and K. S. Seshaiah, *Biol. Pharm. Bull.*, 2003, **26**(9), 1278–1282.
53 M. Al-Obaid, S. G. Abdel-Hameid, H. A. El-Kashef, A. A. M. Abdel-Aziz, A. S. El-Azab, H. A. Al-Khamees and H. I. El-Subbagh, *Eur. J. Med. Chem.*, 2009, **44**, 2379–2391.
54 M. S. Hamed, M. M. Kamel, M. M. Kassem, N. Emad, M. S. Nofal and F. M. Ahmed, *Acta Pol. Pharm.*, 2010, **67**(2), 159–171.
55 V. B. Shashikant, J. D. Bhavana, C. D. Sudarshan, T. G. Suraj, T. R. Vankekesh, V. K. Chetan and P. S. Anik et, *J. Pharmacol. Exp. Ther.*, 2008, **326**(2), 604–613, DOI: 10.1124/jpet.
56 R. Kaur, M. Bansal and B. Kaur, *Chem. Sci. J.*, 2011, CSJ-18.
57 P. S. N. Reddy, M. Vasantha and V. D. Reddy Rasayan, *J. Chem.*, 2010, **3**(4), 635–640.
58 M. Suchy and R. H. E. Hudson, *J. Org. Chem.*, 2014, **79**, 3336–3347, DOI: 10.1021/jo402873e.
59 S. Y. Wang, *J. Org. Chem.*, 1959, **24**, 11–13.
60 C. Ausín, J. A. Ortega, J. Robles, A. Grandas and E. Pedroso, *Org. Lett.*, 2002, **4**, 4073–4075.
61 L. J. Gooβen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662–664.
62 W. Li, X. Zhou, Y. Chen, S. Guo, F. Ba, W. Tian, C. Yang, M. Wang, Y. Liu, Y. Song, J. Zhu, Y. Zhou, F. Zhou, H. Guo and C. Zheng, *Tetrahedron*, 2016, **72**(23), 3185–3192.
63 C. G. Hartung, A. C. Backes, B. Felber, A. Missio and A. Philipp, *Tetrahedron*, 2006, **62**(43), 10055–10064, DOI: 10.1016/j.tet.2006.08.065.
64 P. Yin, N. Liu, Y.-X. Deng, Y. Chen, Y. Deng and L. He, *J. Org. Chem.*, 2012, **77**, 2649–2658, DOI: 10.1021/jo2023697.
65 R. R. Vidule, *Indian J. Appl. Res.*, 2013, **3**(8), 74–77.
66 A. A. F. Wasfy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 1349–1358.
67 K. Špirková and Š. Stankovský, *Collect. Czech. Chem. Commun.*, 1996, **61**, 957–961, DOI: 10.1135/cccc19960957.
68 N. F. Abdel-Ghaffar, *Nat. Sci.*, 2011, **9**(7), 190–201.
69 Q.-Z. Shi, Y.-N. Cao, S.-B. Ma, G.-X. Wang, G.-F. Han and Z. Xing, *J. Chem. Res.*, 2016, **40**, 767–771.
70 S. Venkateswarlu, M. Satyanarayana, P. Ravikiran and V. Siddaiah, *J. Heterocycl. Chem.*, 2013, **50**(5), 1089–1093, DOI: 10.1002/jhet.1603.
71 Š. Stankovský and A. Filip, *Chem. Zvesti*, 1984, **38**(5), 677–685.
72 T. Yoshikawa and K. Shitago, *Yakugaku Zasshi*, 1974, **94**(4), 417–423, DOI: 10.1248/yakushi1947.94.4_417.
73 (*a*) K. Hirota, Y. Kitade, H. Sajiki and Y. Maki, *Synthesis*, 1984, **1984**(7), 589–590, DOI: 10.1055/s-1984-30901; (*b*) K. Hirota, Y. Kitade, M. Sajika and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, 1990, 123–128, DOI: 10.1039/P19900000123.
74 S. K. Srivastava, W. Haq and P. M. S. Chauhan, *Bioorg. Med. Chem. Lett.*, 1999, **9**(7), 965–966, DOI: 10.1016/S0960-894X(99)00128-6.
75 A. M. Hussein, *J. Saudi Chem. Soc.*, 2010, **14**, 61–68.
76 G. H. Elgemeie and H. A. Ali, *Synth. Commun.*, 2002, **32**(2), 253–264, DOI: 10.1081/SCC-120002010.
77 S. A. Ahmed, A. M. Hussein, W. G. M. Hozayen, A. H. H. El-Ghandour and A. O. Abdelhamid, *J. Heterocycl. Chem.*, 2007, **44**(4), 803–810.
78 A. M. Hussein and O. M. Ahmed, *Bioorg. Med. Chem.*, 2010, **18**(7), 2639–2644, DOI: 10.1016/j.bmc.2010.02.028.
79 A. Karoui, F. Allouche, M. Deghrigue, A. Agrebi, A. Bouraoui and F. Chabchoub, *Med. Chem. Res.*, 2014, **23**, 1591–1598, DOI: 10.1007/s00044-013-0742-x.
80 S. Gupta, L. M. Rodrigues, A. P. Esteves, A. M. F. Oliveira-Campos, M. S. Jose Nascimento, N. Nazareth, H. Cidade, M. P. Neves, E. Fernandes, M. Pinto, N. M. F. S. A. Cerqueira and B. Natercia, *Eur. J. Med. Chem.*, 2008, **43**, 771–780, DOI: 10.1016/j.ejmech.2007.06.002.
81 F. Allouche, F. Chabchoub, F. Carta and C. T. Supuran, *J. Enzyme Inhib. Med. Chem.*, 2013, **28**, 343–349, DOI: 10.3109/14756366.2012.720573.
82 M. Bakavoli, G. Bagherzadeh, M. Vaseghifar, A. Shiria, M. Pordel, M. Mashreghi, P. Pordeli and M. Araghi, *Eur. J. Med. Chem.*, 2010, **45**, 647–650, DOI: 10.1016/j.ejmech.2009.10.051.

83 C. E. Mueller, D. Shi, M. Manning Jr. and J. W. Daly, *J. Med. Chem.*, 1993, **36**(22), 3341–3349, DOI: 10.1021/jm00074a015.
84 A. M. Hayallah, J. Sandoval-Ramírez, U. Reith, U. Schobert, B. Preiss, B. Schumacher, J. W. Daly and C. E. Müller, *J. Med. Chem.*, 2002, **45**(7), 1500–1510, DOI: 10.1021/jm011049y.
85 S. Weyler, A. M. Hayallah and C. E. Muller, *Tetrahedron*, 2003, **59**, 47–54, DOI: 10.1016/S0040-4020(02)01485-0.
86 S. Weyler, F. Fülle, M. Diekmann, B. Schumacher, S. Hinz, K. N. Klotz and C. E. Müller, *ChemMedChem*, 2006, **1**(8), 891–902, DOI: 10.1002/cmdc.200600066.
87 O. M. Abo-Salem, A. M. Hayallah, A. Bilkei-Gorzo, B. Filipek, A. Zimmer and C. E. Müller, *J. Pharmacol. Exp. Ther.*, 2004, **308**(1), 358–366, DOI: 10.1124/jpet.103.056036.
88 S. H. Abdel-Hafez, R. A. Ahmed, M. A. Abdel-Azim and K. M. Hassan, *J. Chem. Res.*, 2009, **2009**, 56–59.
89 V. D. Dyachenko and V. P. Litvinov, *Russ. Chem. Rev.*, 1997, **66**(11), 923–951, DOI: 10.1070/RC1997v066n11ABEH000323.
90 P. R. Murumkar, M-Pharm, thesis submitted to North Maharastra University, Jalgaon, 2004.
91 S. Von Niementowski, *J. Prakt. Chem.*, 1895, **51**, 564–572.
92 S. S. Laddha and S. P. Bhatnagar, *ARKIVOC*, 2007, (xvi), 1–11, DOI: 10.3998/ark.5550190.0008.g01.
93 A. M. Abdel-Fattah, A. S. Aly, F. A. Gad, N. A. Hassan and A. B. A. El-Gazzar, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **163**, 1–27.
94 R. O. Bora, I. S. Rathod, S. S. Toshniwal and M. Farooqui, *Int. J. Chem. Sci.*, 2005, **3**(3), 469–474.
95 A. S. Aly, A. B. A. El-Gazzar and H. A. R. Hussein, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2007, **182**, 35–56, DOI: 10.1080/10426500600865293.
96 S. S. Laddha and S. P. Bhatnagar, *ARKIVOC*, 2008, (xvii), 212–220, DOI: 10.3998/ark.5550190.0009.h20.
97 A. A. Abu-Hashem, *Molecules*, 2018, **23**, 2793–2812, DOI: 10.3390/molecules23112793.
98 A. Abu-Hashem and M. M. Youssef, *Molecules*, 2011, **16**, 1956–1972, DOI: 10.3390/molecules16031956.
99 J. C. Burbiel, J. Hockemeyer and C. E. Müller, *Beilstein J. Org. Chem.*, 2006, **2**(1), 20–25, DOI: 10.1186/1860-5397-2-20.
100 J. Garín, E. Meléndez, F. L. Merchán, D. Ortiz and T. Tejero, *Synthesis*, 1987, **1987**(4), 368–370, DOI: 10.1055/s-1987-27946.
101 R. J. Cruickshank; P. Duguid; R. R. Swain *J. Med. Microbiol.*, Vol. 1, New York: Churchill Livingstone Publishers, 1998.
102 O. M. Ahmed, A. M. Hussein and R. R. Ahmed, *Med. Chem.*, 2012, **2**(1), 020–028, DOI: 10.4172/2161-0444.1000108.
103 S. S Laddha and S. P Bhatnagar, *Future Med. Chem.*, 2010, **2**(4), 565–573, DOI: 10.4155/FMC.10.16.
104 S. S. Laddha, S. P. Bhatnagar, Novel Fused quinazolinones: Further studies on the anticonvulsant activity of 1,2,9,11 tetrasubstituted-7H-thieno[2′,3′:4,5]pyrimido[6,1-b]-quinazolin-7-one and 1,3,10,12-tetra-substituted-8H-pyrido[2′,3′:4,5]pyrimido[6,1-b]quinazolin-8-one. *13rd International Electronic Conference on Synthetic Organic Chemistry (ECSOC-13)*, November, 2009, pp. 1–30.
105 M. Shibuya, *J. Biochem.*, 2013, **153**(1), 13–19, DOI: 10.1093/jb/mvs136.
106 S. Guo, L. S. Colbert, M. Fuller, Y. Zhang and R. R. Gonzalez-Perez, *Biochim. Biophys. Acta*, 2010, **1806**(1), 108–121, DOI: 10.1016/j.bbcan.2010.04.004.
107 K. J. Griessmeier and C. E. Müller, *Pharmacology*, 2005, **74**, 51–56, DOI: 10.1159/000083983.

